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Synthesis of secondary amines

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1. Introduction

Syntheses of amines have perhaps received more attention than the preparation of many other functional groups in organic chemistry.[1] With the growing repertoire of biologically relevant nitrogenous molecules, so is the need for efficient synthetic methods to prepare amines as useful intermediates.[2,3] Due to their interesting physiological activities, secondary amines in particular are extremely important pharmacophores in numerous biologically active compounds, which have greatly been touted in the area of drug discovery.[4] This field has also spurred intense activity on solid phase synthesis[5] as well as combinatorial library

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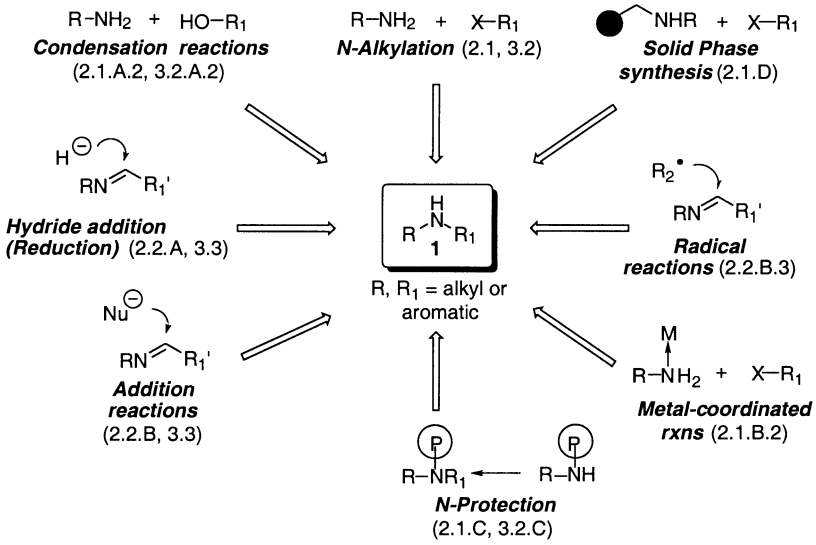


Scheme 1.

generation,[6] where the secondary amine can be utilized as an important scaffolding for further manipulations. However, despite the widespread interest, traditional methods for secondary amine formation are often problematic because of harsh reaction conditions, generally poor yields, and/or low chemical selectivities.[7] Illustrated in Scheme 1 is a brief classification for the major traditional methods for the synthesis of secondary amines, among which suitable procedures and conditions can be properly chosen to prepare the desired amines efficiently. The purpose of this review is to provide a general overview for the formation of secondary amines utilizing pertinent examples highlighted from the literature, while discussing perspectives in the future development of improved methodologies and conditions for this functionality.

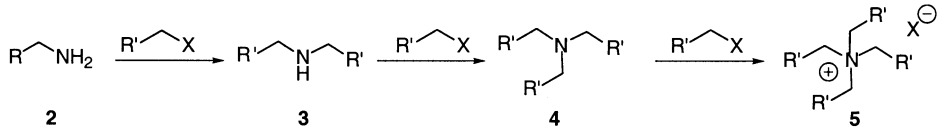
2. Preparation of secondary alkyl amines

2.1. *N*-Alkylation of primary amines

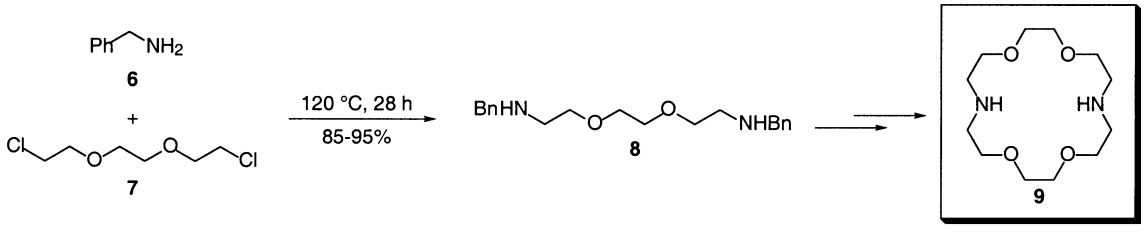
2.1.1. Unactivated amines

2.1.1.1. With alkyl halides. Direct *N*-alkylation is, in principle, the most common and straightforward route to secondary amine formation (Scheme 2).[8] Treatment of primary amines with alkyl halides, or their equivalents (e.g. dialkyl sulfates or sulfonates) is commonly known as the 'Hofmann alkylation'.[9] However, although the conversion appears deceptively simple, it is well known that the synthetic value of this method is limited due to the concomitant overalkylations, giving rise to mixtures of primary, secondary, and tertiary amines, as well as quaternary ammonium salts.[3] Traditionally, secondary amine **3** can be obtained predominantly by treatment of an alkyl halide with a large excess of a primary amine **2**.[10] This is usually an expensive and wasteful process, especially when chiral amines are employed. Consequently, reaction yields typically vary depending on the nature of the amines used, and the excess quantity of starting amines **2** must be removed (normally by distillation techniques).

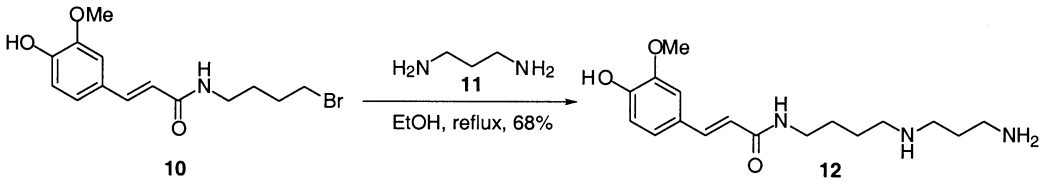
For example, Gatto and co-workers prepared 1,10-dibenzyl-4,7-dioxa-1,10-diazadecane (**8**) in high yield by the simple treatment of 1,2-bis(2-chloroethoxy)ethane (**7**) with a 16-fold excess of benzylamine (**6**) at elevated temperature (Scheme 3).[11] An excess of the starting amine certainly aided in suppressing overalkylations, and the remaining benzylamine was subsequently removed by vacuum



Scheme 2.



Scheme 3.



Scheme 4.

distillation. This intermediate **8** was used as a crucial template in the synthesis of 4,13-diaza-18-crown-6 (**9**), which is known to possess metal chelation properties.

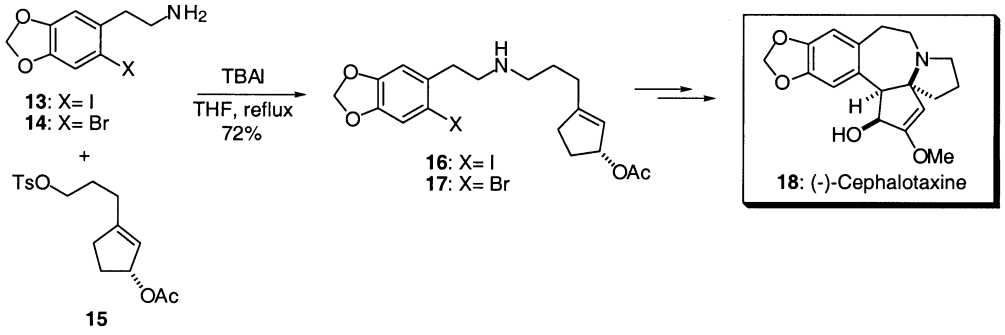
Diamines and polyamines can also undergo mono-*N*-alkylation. Under similar reaction conditions, Ramiandrasoa carried out an efficient synthesis of N^8-ferulylspermidine (Scheme 4).[12] Treatment of bromide **10** with excess 1,3-diaminopropane (**11**) in refluxing ethanol smoothly afforded the mono-acyl triamine **12** in 68% yield. Using an overabundance of the diamine, *N*-alkylation was chemoselective, and 1,4-addition was circumvented.

Since alcohols are amongst the most versatile starting materials in organic synthesis, masked alcohols such as sulfonates, alkyl phosphates, and alkyl phosphites, are known to act as suitable leaving groups in *N*-alkylation reactions.[13] Nonetheless, direct mono-*N*-alkylations with such leaving groups often require harsh reaction conditions. Simple reflux temperatures suffice for higher boiling amines but applied pressure is necessary for lower boiling amines.

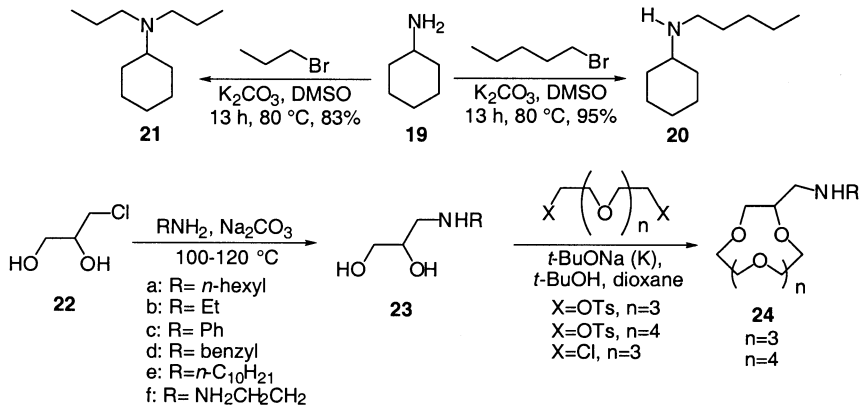
In the Tietze synthesis of (−)-cephalotaxine (**18**), primary amines **13** and **14**, respectively, underwent facile alkylations with tosylate **15** after in situ conversion to the corresponding iodo compound using tetrabutylammonium iodide in the absence of any additional base (Scheme 5).[14] Several attempts were made to improve the yields by adding varying amounts of triethylamine or Hünig's base. Nevertheless, the yields were best if the primary amine was used in 2–3 fold excess. As a result, secondary amines **16** and **17** were obtained in 70–90% yields, offering the proper functionalities for Pd-catalyzed cyclization to form the desired spirocyclic amine moiety of (−)-cephalotaxaine.

A common misconception that arises is employment of the alkylating agent as the limiting reagent is sufficient for the selective synthesis of secondary amines. However, even if the electrophile is present in a limiting amount, the equilibrium between the protonated product and the starting amine is rapid enough to result in a complex mixture of products, which renders this protocol far from general.[15] Therefore, through careful adjustment of reaction parameters such as the relative proportions of the reactants,[16] reaction temperature,[17] time,[18] and the use of additives,[19] one can tune conditions accordingly, so that the secondary amine becomes predominant. In addition, other constraints such as amine basicity,[20] steric demands,[21] and relative solubilities in solvent media,[22] and so forth need to be taken into account if product yields are of importance. For example, the alkylation of a sterically hindered amine such as *tert*-butylamine will proceed to the secondary amine exclusively using benzyl chloride.[23] Steric hindrance near the amine nitrogen protects against formation of the tertiary amine or quaternary ammonium salts.

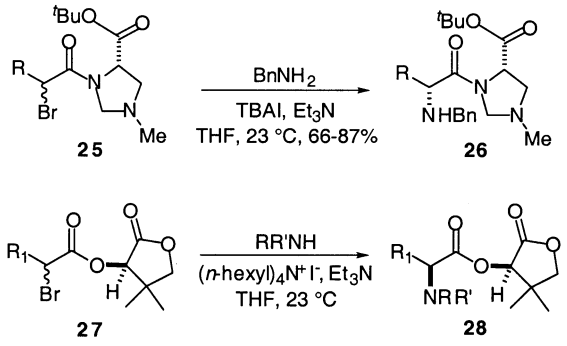
Another common protocol includes the presence of an inorganic base to affect the aforementioned transformation. The most conventional conditions utilize an alkali metal carbonate (e.g. K_2CO_3) in a polar aprotic solvent (DMF, DMSO, or MeCN) at room temperature or under heating, depending on the nature of the starting materials. Typically, an equimolar ratio of an amine, an alkyl halide, and a base is utilized, although variations in this recipe have been reported. As an example, Srivastava observed that *N*-alkylation with primary alkyl halides in DMSO using K_2CO_3 as the base offered an opportunity to obtain either dialkyl or trialkylamines selectively, by varying the nature of the electrophile used in the reaction (Scheme 6).[24] It was also observed that the course of the alkylation was strongly dependent on the number of carbon atoms present in the alkyl bromide. Alkyl bromides of longer chain length (≥5 carbons), such as *n*-pentyl bromide, underwent alkylation efficiently with cyclohexylamine (**19**) to afford monoalkylamine **20** exclusively. Conversely, use of smaller chain



Scheme 5.



Scheme 6.



Scheme 7.

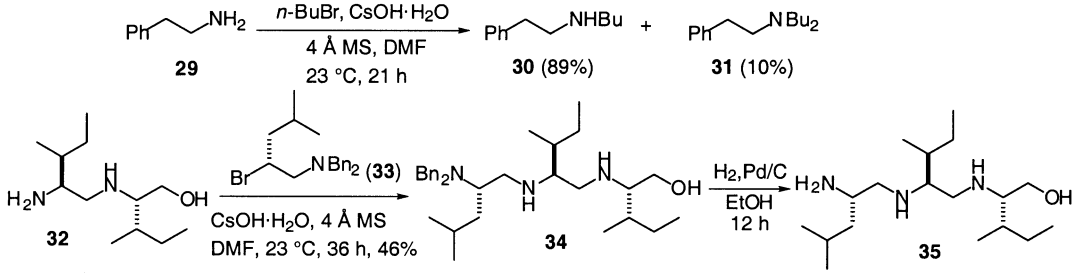
lengths (<5 carbons, e.g. *n*-propyl bromide) reversed the selectivity, giving rise to *N*,*N*-dialkylamines **21**, and no monoalkylamine was detected.

In light of these results, Okahara used Na_2CO_3 as the base in a solvent-free selective *N*-alkylation of 3-chloro-1,2-propanediol (**22**) with various primary amines employed in excess amounts.[25] These conditions gave rise to the corresponding secondary amines accordingly. Further functionalization of the 3-(*N*-substituted amino)-1,2-propane diols **23** led to practical syntheses of aminomethyl crown ethers **24**. During the investigation of the scope of this procedure, it was found that pendant hydroxyl groups on **23** were left intact, which offers a considerable advantage if alcohol functionality is needed for further synthetic manipulations.

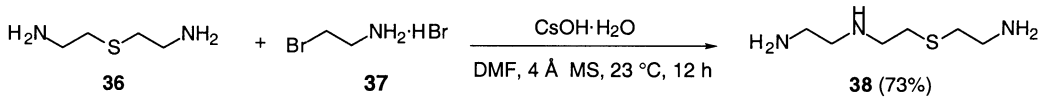
Organic bases can also be used to carry out the same transformation in the similiar manner. For example, O'Meara utilized triethylamine in the presence of a phase transfer catalyst (tetrabutylammonium iodide) for the *N*-benzylation of diasteromeric α-halo imides **25** at room temperature (Scheme 7).[26] The corresponding (*S*,*S*)-diastereomer of α-benzylaminoimidazolidones **26** were isolated in 66–87% yields and in >99% ee. In a similar fashion, Durst reported a serendipitous synthesis of *N*-protected optically active α-amino esters **28** from racemic α-halo pantolactone esters **27** using a similar kinetic resolution protocol.[27] In both cases, the highly diasteroselective nucleophilic displacement by the amine was attributed to use of the chiral imidazolidinone auxiliary, which is easily cleaved under standard reaction conditions. This method offers widespread applications in asymmetric organic synthesis. Nonetheless, racemization of chiral substrates under these conditions is always a potential problem.

A displacement reaction of a suitable leaving group by an amine can also occur in strongly basic media. However, avoidance of dehydrohalogenation of the starting alkyl halide is of prime concern.[28] For instance, lithium naphthalenide has been exploited for selective *N*-alkylation of various primary amines using alkyl halides at room temperature.[29] In such experiments, amines were used in stoichiometric amounts, but the yields were typically no greater than 50% mainly due to eliminations. Most alkali bases including powdered KOH can be used in the same manner, however selectivity between the dialkyl and trialkylamines is usually poor.

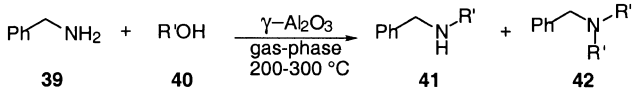
Recently, Jung and co-workers provided an alternative solution to this chronic problem of using primary amines as limiting reagents (Scheme 8).[30] Employing cesium hydroxide, *N*-alkylation was efficiently carried out affording



Scheme 8.



Scheme 9.



Alcohol (**40**)	T (°C)	Yield of **41**	Yield of **42**
n-prOH	300	77	5
2-propanol	230	80	20

Scheme 10.

various secondary amines. A cesium base was observed not only to promote mono-*N*-alkylations, but also to suppress overalkylations, favoring secondary amine formation over tertiary amines in the presence of activated 4 Å molecular sieves. As represented in Scheme 8, *N*-alkylation of phenethylamine (**29**) with 1-bromobutane produced secondary amine **30** in high yield. A noteworthy feature embodied in this protocol is the selective *N*-alkylation of amino acid derivatives. Using this methodology, *N*-alkylation of amino alcohol **32** with secondary bromide **33** was favored over the competing *O*-alkylation. Thus, higher order peptidomimetic **35** was synthesized efficiently after hydrogenolysis of the benzyl groups from trimer **34**.[31]

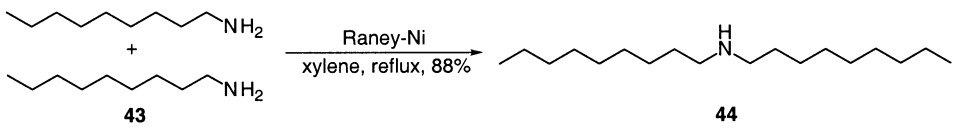
As an extension of this method, *N*-alkylation of diamines and polyamines also afforded excellent selectivities, generating mono-*N*-alkylation products in high yields.[31] As represented in Scheme 9, diamine **36** was directly *N*-alkylated using 2-bromoethylamine·HBr (**37**) in the presence of cesium hydroxide. After 12 h, polyamine **38** was isolated in 73% overall yield, exhibiting high selectivity in favor of monoalkylation.

2.1.1.2. With alcohols. The principle of direct alkylation of amines with alcohols is known since the beginning of the century, but the reactions typically proceed only in the presence of a metal catalyst. The first *N*-alkylation of amines was performed using alcohols and ThO_2 as a catalyst, but reaction conditions were often difficult to apply.[32] Furthermore, there are only a few examples in the literature describing the alkylation of aliphatic amines with alcohols. A typical one is the methylation of *n*-butylamine using methanol, however, the selectivity is directed towards the dimethylated product.[33] Alcohols have also been condensed with amines using transition metal catalysts such as nickel,[34] rhodium,[35] or ruthenium.[36] Although these methods are selective towards mono-*N*-alkylation, the major drawback is that they proceed in a homogeneous phase where separation procedures for removing and recycling the catalyst are tedious in nature. As addressed in Scheme 10, Valot recently reported a gas phase selective *N*-alkylation of benzylamine (**39**) with various alcohols **40** using γ-alumina.[37] High selectivity in favor of the monoalkylated product **41** was found. This procedure is applicable for a large number of alcohols and amines. As additional benefits, the reaction conditions are solvent-free, and cheap γ-alumina offers a suitable replacement for expensive metal catalysts.

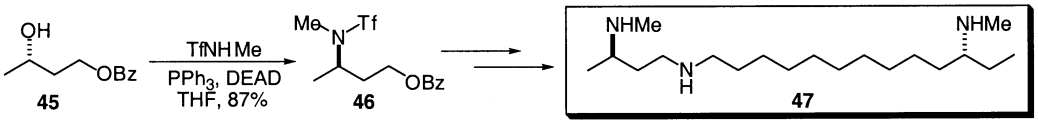
As an extension of this method, there are scattered reports in which primary amines self-condense. To carry out such condensations, high hydrogen pressure is often needed, which is a drawback.[38] De Angelis and co-workers developed an interesting method in which primary amines containing α-hydrogens self-condense to generate symmetrical secondary amines, which averted the use of alcohols.[39] As demonstrated in Scheme 11, cross condensations of aliphatic amines such as *n*-nonylamine (**43**) generated the aliphatic dialkylamines **44** along with unreacted starting material and evolution of ammonia. Refluxing xylene was found to be the solvent of choice, where other solvents offered decreased yields. Cycloalkylamines and reactive amines such as benzylamine also proved pragmatic. In all studied cases, tertiary amine formation was completely averted.

2.1.2. Activated amines

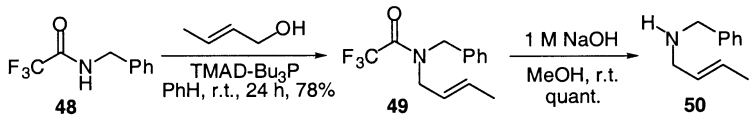
2.1.2.1. Covalent derivatives. *N*-Protected primary amines are common intermediates which are widely utilized as synthons in numerous organic syntheses. A popular transformation involving a covalently activated amine derivative is the Mitsunobu reaction. This conversion involves the condensation between a component possessing an acidic



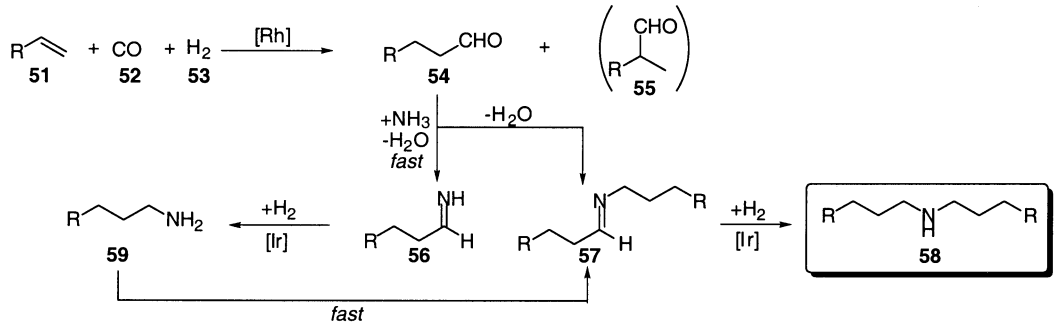
Scheme 11.



Scheme 12.



Scheme 13.

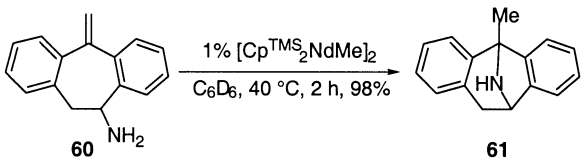


Scheme 14.

proton (e.g. a sulfonamide) and a primary or secondary alcohol in the presence of diethylazodicarboxylate (DEAD) and triphenylphosphine.[40] As shown in Scheme 12, Edwards reported a reaction of *N*-methyltrifluoromethanesulfonamide (TfNHMe) with benzoyl protected alcohol **45**, which gave triflate protected amine **46** in high yield.[41] Further treatment of **46** with 1,7-bis-(trifluoromethanesulfonamido)heptane under these Mitsunobu conditions gave antitumor polyamine **47** after a series of synthetic sequences. However, the drastic reduction procedures (e.g. Na/NH_3) exploited in this synthesis can often cause epimerization.

To avoid such complications, more versatile Mitsunobu reagents can be used. Tsunoda shortly thereafter developed a new reagent, *N*,*N*,*N*′,*N*′-tetramethylazodicarboxamide (TMAD), in application toward the synthesis of secondary amines.[42] This reagent was found to be more versatile than the more traditional reagent (DEAD), and was utilized in combination with Bu_3P. Use of TMAD or other azodicarboamides such as 1,1′-(azodicarbonyl)dipiperidine (ADDP)[43] and tetraisopropylazodicarboxamides (TIPA)[44] were also investigated, and were found to be superior to DEAD. An efficient alkylation with TMAD–Bu_3P of trifluoroacetamide **48**, shown in Scheme 13, provides an *N*-(2*E*)-crotylacylamide (**49**), which can be easily hydrolyzed in quantitative yield under mild reaction conditions to give pure benzyl-(2*E*)-crotylamine (**50**).[45] This represents an excellent method for the synthesis of allylic secondary amines, which are of particular value in organic synthesis.

Hydroaminomethylation of olefins to amines represents an economically efficient and elegant synthesis of aliphatic

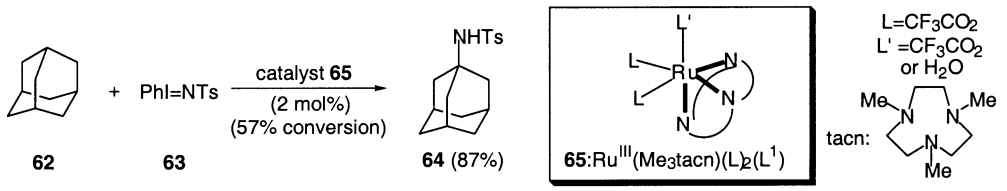


Scheme 15.

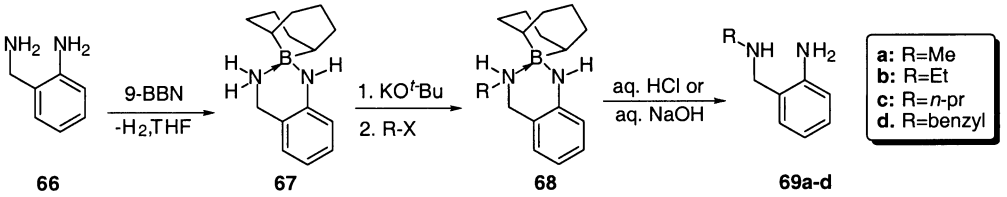
secondary amines.[46] In hydroaminomethylation, a reaction sequence of hydroformylation of an olefin to an aldehyde, followed by reductive amination, proceeds in a cascade reaction fashion. Recently, Beller for the first time described the highly selective hydroaminomethylation of olefins with ammonia to form linear secondary aliphatic amines using a new Rh/Ir catalyst system (Scheme 14).[47] Both primary amine **59** and secondary amine **58** can be formed with greater than 90% selectivity, and reaction conditions can be tuned to afford secondary amines by simple variation of the olefin/NH_3 ratio. As mechanistically demonstrated, when 0.5 equiv. of NH_3 is used per equivalent of olefin **51**, half of the aldehyde **54** reacts with the ammonia and half with the newly formed primary amine **59**, leading to preferential formation of the secondary amine **58**. In a similar way, Eilbracht explored a selective one-pot synthesis of symmetrically and unsymmetrically substituted amines via rhodium catalyzed multiple alkylations using primary amines under hydroformylation conditions.[48]

Alongside hydroaminomethylation, hydroamination also proves to be an elegant route towards secondary amines as well.[49] Recently, Molander and co-workers utilized a lanthanide-catalyzed hydroamination of hindered alkene **60** in the synthesis of the tetracyclic amine MK-801 (**61**) (Scheme 15).[50]

Direct introduction of the amine moiety to an alkyl substrate is an important synthetic transformation in organic chemistry however very difficult to carry out. As mentioned above, hydroaminomethylation and hydroamination are two popular methods for secondary amine formation. In addition, the selective amination of unfunctionalized hydrocarbons in the presence of metal catalysts constitutes an appealing route for the synthesis of dialkylamines.[51] Amination reactions have been reported involving olefins and metal catalysts, and notably, direct amidations of hydrocarbons have also been achieved. For example, Che recently reported an efficient catalyzed selective amidation of a series of unfunctionalized hydrocarbons using PhI=NTs as the nitrogen source, in the presence of ruthenium complexes **65**.[52] A notable example which offered high



Scheme 16.

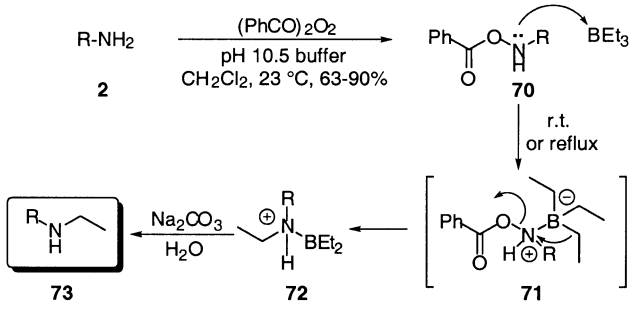


Scheme 17.

selectivity was adamantane (**62**), in which the tertiary C–H bonds were exclusively amidated to give *N*-Ts adamantane (**64**) in 87% yield (Scheme 16). Alkylation followed by Ts-deprotection offers an intriguing route to secondary amines beginning from hydrocarbon sources.

2.1.2.2. Metal-coordinated amines. In principle, *N*-chelation to a metal typically renders the amine non-nucleophilic since the nitrogen lone pair is involved in coordination to the metal atom. However, coordinated amines still show nucleophilic properties, which can be used as an advantage, since the nucleophilicity is not as great when compared to the free amine.[53] Consequently, the alkylation of a coordinated amine rarely proceeds beyond the monoalkyated stage in contrast to *N*-alkylation of free amines.

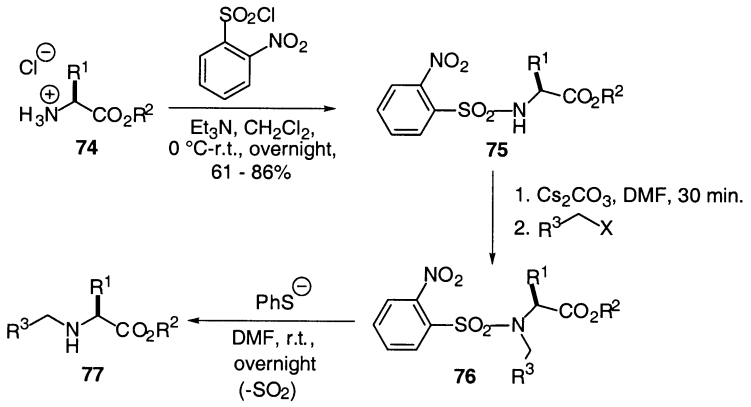
For example, coordination of ethylenediamine to a metal such as rhodium sufficiently deactivates the amine so that monoalkylation may be achieved in a selective manner. $[Rh(en)_3)]^{3+}$ salts have been reported to react with methyl iodide to give the corresponding *N,N′*-dimethyl-1,2-diaminoethane.[54] In contrast, as demonstrated in Scheme 17, Kol recently described the first practical method for an N-alkylation relying on an amine-aminoborane chelate formed from the reaction of 9-BBN with 2-aminobenzylamine (**66**).[55] In this system, *N*-chelation to the boron atom increases the acidity of the NH_2 protons in **67**, which was treated with potassium *tert*-butoxide followed by subsequent alkylation with an alkyl halide to provide **68**. Finally, mild hydrolysis of the 9-BBN yielded the desired 2-amino-*N*-alkyl benzyl secondary amines **69** in nearly quantitative yields. Alkylation was found to be completely regioselective on the benzylic nitrogen, and no polyalkylated products were formed.



Scheme 18.

Alternative methods using organoboron methodology allows access to substituted and protected amines by various other routes. Brown led pioneering expeditions in this field and numerous reviews on the topic have been written.[56] Furthermore, secondary amines can be generated via *N*-chloro derivatives of primary amines[57] or through the use of organic azides using trialkylboranes.[58] Nonetheless, these nitrogen-based reagents lack general use due to their instability and hazardous nature. Recently, Phanstiel reported a synthesis of secondary amines via *N*-(benzoyloxy)amines using organoborane reagents as delineated in Scheme 18.[59] A variety of primary amines **2** were converted to the *N*-(benzoyloxy)amines **70** via in situ oxidation using buffered benzoyl peroxide. In the presence of triethylborane (1 M), these 'activated amines' were transformed into their *N*-ethylamine derivatives **73**, where the *N*-ethylation step was reported to be highly dependent on steric flanking of the R group.

2.1.3. Protected amines. Due to the highly basic and nucleophilic nature of the lone pair of electrons on the nitrogen atom, primary amines are known to be an extremely reactive functionality, which can cause interference in synthetic transformations. Due to the high reactivity, direct alkylations as elaborated upon (cf. Section 2.1) often suffer from poor selectivity, and thus it is usually necessary to transform the amine into a derivative in order to reduce amine nucleophilicity.[60] By forming an ammonium salt, the usual reactions involving amines (e.g. alkylation and oxidation) are not possible. Although ammonium salts are not often used as protecting groups, a variety of options exists for altering the reactivity of a primary amine. Discussed below, although not exhaustive, are examples of frequent reactions involving common protected secondary amines. General reviews on amino protecting groups are available,[61] and should be consulted for more specific situations.



Scheme 19.

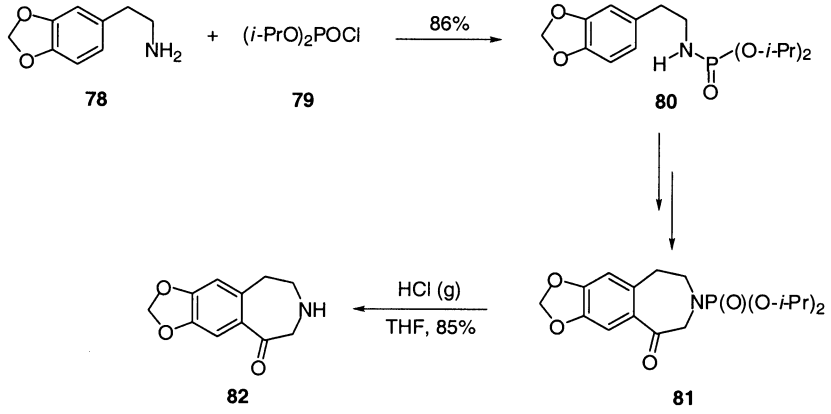
Amongst many derivatizations, carboxamide and sulfonamide are one of the most useful protecting strategies.[62] Although widely used, these processes suffer from the disadvantage that in some cases, alkylation yields are low and these groups are often difficult to remove. Common deprotection strategies usually require brute force by heating in strongly acidic or basic media to effect necessary cleavages. Simple amides (e.g. formamide, acetamide, benzamide) are usually prepared from the reaction of the corresponding acid chloride or the anhydride with the amine, catalyzed by a base.[63] Numerous imaginative amide-type protecting groups have been developed.[64]

Fukuyama and co-workers introduced the 2-nitrobenzenesulfonyl group as a new amine protecting/activating group.[65] Since then, this group has enjoyed much success for the synthesis of a variety of secondary amines as well as numerous natural products. Selective diamine protection has also proved fruitful by utilizing this method. As a selected example, Bowman reported a monoalkylation of the amino group using α-amino esters facilitated by the use of nitrophenylsulfonamide (Ns) protecting group (Scheme 19).[66] Addition of 2-nitrobenzenesulfonyl chloride (NsCl) to an ice-cooled solution of the amino ester **74** with Et_3N generated the corresponding sulfonamide **75**. Formation of the anion of the sulfonamide using Cs_2CO_3 and subsequent alkylation gave intermediate **76**. Facile removal of the sulfonyl group using phenylthiolate anion yielded the N-monoalkylated α-amino acid derivatives **77**, respectively.

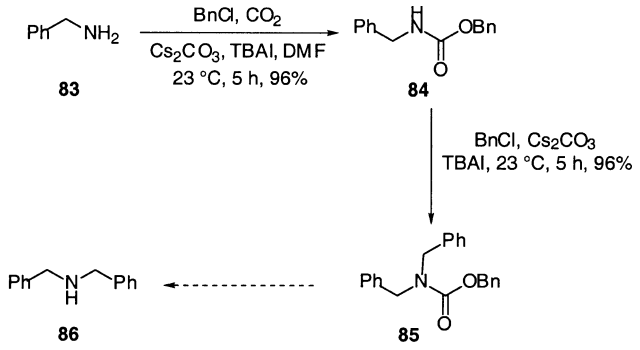
Reminiscent of sulfonamides, phosphoramidates are derivatives which have been largely used for the protection of amines and amino acids.[67] In particular, dialkylphosphoramidates are easily generated, typically with use of a dialkylchlorophosphate and Et_3N in methylene chloride. Furthermore, cleavage of the phosphoramidate with HCl-saturated THF proceeds in high yield.[68] In addition, their stability is generally good to organic and Lewis acids. As illustrated in Scheme 20, primary amine **78** reacted with diisopropyl chlorophosphate (**79**) to generate the phosphoramidate **80**, which upon ring closure to **81** followed by deprotection afforded the cyclic secondary amine **82** in high yield.[68]

More labile *N*-protecting groups such as the carbamate moiety, have enjoyed popularity, specifically in amino acid chemistry and peptide synthesis.[69] Since a plethora of carbamate-based amino protecting groups exist, we will limit our on-going discussion to those examples most commonly used in organic synthesis. References regarding protecting groups that seem to have more limited use should be consulted accordingly.

The most widespread application of the benzyloxy carbonyl (Cbz) group is in the protection of primary and secondary amines. This moiety is easily installed by the reaction of an amine with benzyl chloroformate in the presence of a base (aqueous carbonate or Et_3N/CH_2Cl_2).[70] After protection, the protected amine can be utilized in standard amino acid



Scheme 20.

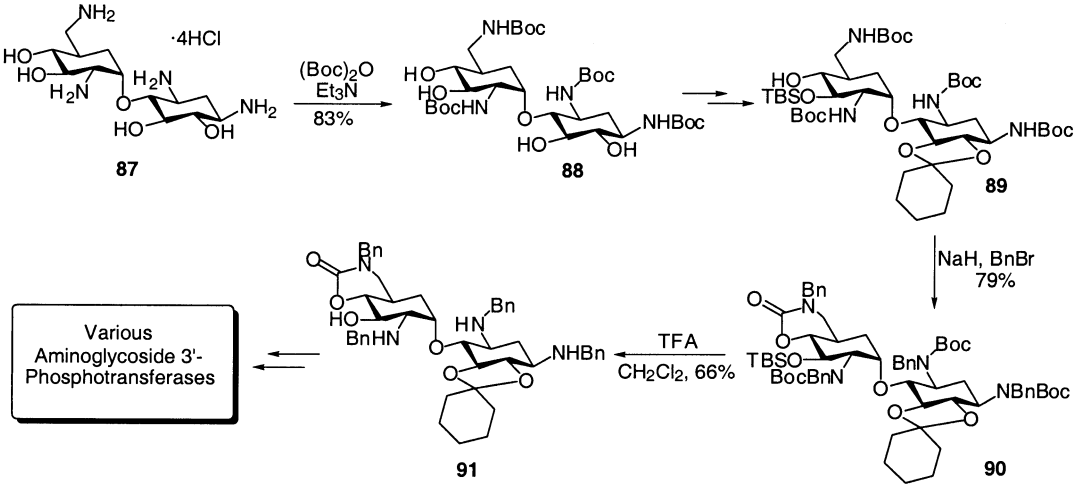


Scheme 21.

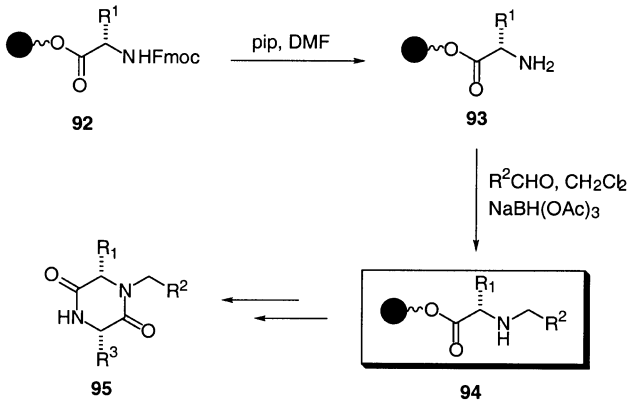
coupling reactions. This group is known to be very stable to acids and bases, to nucleophiles, to mild Lewis acids, and to most metal hydrides. However, its utility lies in its lability toward removal by catalytic hydrogenation, and hydrogenolysis using hydrogen donors such as ammonium formate or formic acid with Pd/C. A wide variety of primary and secondary aliphatic and aromatic amines can be selectively protected in the presence of other functionality, such as alcohol or thiol. As a synthetic example, Jung and coworkers generated Cbz-protected benzylamine (**84**) using a safer and milder protocol, via a three component coupling of an amine, CO_2, and an alkyl halide in the presence of a cesium base.[71] Upon installation of the Cbz-protecting group, subsequent alkylation of the masked amino group with benzyl chloride using Cs_2CO_3 and tetrabutylammonium iodide (TBAI) gave rise to the *N*,*N*-dibenzylcarbamate **85** quickly in high yield (96% yield after 5 h).[72] Upon removal of the Cbz moiety (hydrogenolysis), the corresponding dibenzylamine (**86**) can be easily generated (Scheme 21).

Another widely used carbamate protecting group is the *tert*-butyl carbamate (or *t*-butoxycarbonyl) commonly referred to as the ^{t}Boc group.[73] Boc groups are introduced by reaction of amines with Boc anhydride or chloride under basic conditions. Preparation from the mixed carbonate ester known as 'Boc-On' also gives rise to the protected amine.[74] This group is sensitive to strong acid, but is known to be stable to nucleophiles, organometallic reagents, hydrogenation, hydrides, oxidizing agents, and mild Lewis acids. Removal of this group is easily performed by treatment with aqueous HCl, TFA, or *p*-TSA. A synthetic example utilizing Boc protected primary amines was recently reported by Mobashery in the synthesis of inhibitors of aminoglycoside 3′-phosphotransferases (Scheme 22).[75] Upon treatment of neamine hydrochloride (**87**) with di-*tert*-butyl dicarbonate, the tetra-*N*-Boc protected derivative **88** was obtained in high yield using Et_3N. *N*-Benzylation of the TBS-protected 5,6-cyclohexylidene derivative **89** was accomplished using sodium hydride and benzyl bromide to yield cyclic carbamate **90**. Simultaneous removal of the Boc group and the cyclohexylidene moiety was accomplished using trifluoroacetic acid, affording intermediate **91**.

Another base-labile amino protecting group used to mask primary (and secondary) amines is the 9-fluorenylmethyl carbamate (Fmoc) group, which is most commonly used in solution phase synthesis of peptides and has also been adapted to solid phase peptide synthesis.[76] Solid-phase synthesis of peptides using Fmoc protection is rapidly augmenting and/or replacing older methods based on Boc or Cbz protection. The major advantage offered by the use of Fmoc protection is that repetitive treatment with TFA or other strong acids such as HF is no longer required for deprotection. Fmoc protection of amino acids is accomplished by Schotten–Bauman conditions (e.g. $NaHCO_3$/dioxane/H_2O or $NaHCO_3$/DMF) or under anhydrous conditions such as py/CH_2Cl_2 at or below room temperature. Although popular, many chemists no longer use the commercially available chloroformate ester (Fmoc-Cl), but prefer the more stable carbonate form Fmoc-OSu, or Fmoc-pfp.[77] The Fmoc group undergoes rapid non-hydrolytic cleavage on treatment with amine bases (ammonia, piperidine, morpholine) usually in polar solvents such as DMF or MeCN, and the amine product is liberated as its neutral form. Other bases have included DBU and TBAF. The solid phase synthesis of a dioxopiperazine library **95** was recently described,[78] which employed the use of the Fmoc protecting group. Beginning with the corresponding Fmoc protected amine **92**, which was used in previous



Scheme 22.



Scheme 23.

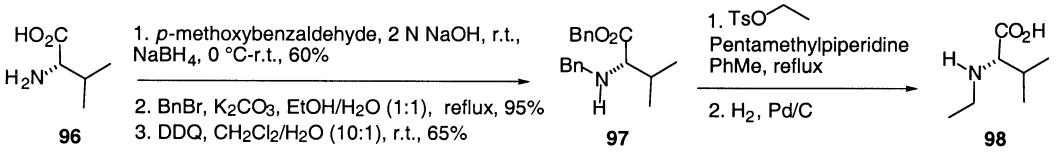
syntheses by the authors, the protecting group was easily unmasked using piperdine in DMF to generate the free amine **93**. The key step was the reductive alkylation with sodium triacetoxyborohydride, which cleanly afforded the polymer-bound secondary amine **94**. Further manipulation of the secondary amine scaffolding of **94**, followed by cyclization, can yield dioxopiperazines in good yields (Scheme 23).[78]

Although not as popular, numerous other carbamates in which the *O*-alkyl bond can be easily cleaved can serve as amino protecting groups. Allyloxycarbonyl, or Alloc,[79] is a representative example, which is typically installed using Alloc-Cl and pyridine, or $Alloc_2O$ in aqueous dioxane under reflux or dichloromethane at ambient temperature. Alloc can be cleaved by a combination of tributyltin hydride in the presence of a Pd(II) catalyst, or through use of a variety of other conditions, such as hydrolysis.[79] The reaction involves the liberation of the carbamic acid after oxidative addition to the palladium. The allylpalladium species can then be reductively cleaved using the stannane, but other procedures for deallylation are available.[79]

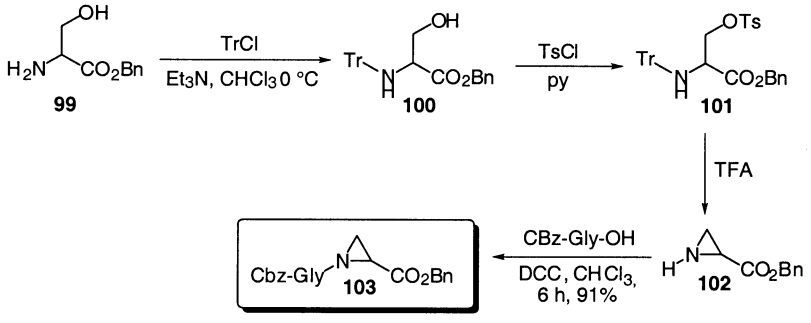
The synthesis of another interesting target possessing a secondary amine involves the use of the 2,2,2-trichloroethylcarbamate (Troc) amino protecting group.[80] Common protocols for installation of the Troc group onto a free primary amine involves the use of TrocCl and pyridine in dichloromethane. Removal conditions typically involve use of Zn dust, and furthermore, under these conditions the Troc group can be selectively cleaved in the presence of Boc, benzyl, and trifluoroacetamido groups offering momentous applications in organic synthesis.[81]

A very popular alkyl group-based protecting group for nitrogen is benzyl (*N*-Bn), and this group has been used extensively in synthetic organic chemistry.[82] This moiety is highly stable to bases, acids, nucleophiles, organometallics, hydrides, and Lewis acids. The group is easily unmasked by two common cleavage methods, catalytic hydrogenation (e.g. H_2 and Pd/C) and dissolving metals (Na/NH_3). As illustrated in Scheme 24, valine (**96**) was treated with *p*-methoxybenzaldehyde to install the PMB unit, which is easily cleavable with suitable oxidants. Subsequent treatment with benzyl bromide in the presence of refluxing aqueous potassium carbonate[83] gave *N*-benzyl-PMB-protected valine benzyl ester, which upon oxidative removal of the PMB using DDQ gave **97**.[84] Addition of excess halide and/or base to the free primary amine (prior to PMB protection) often leads to *N*,*N*-dibenzyl derivatives, which have also been well explored. Chemoselective removal of one benzyl group is possible to give the *N*-monobenzyl derivatives which can also be utilized as a scaffolding in further syntheses.[85] The PMB group in this particular example, was exchanged for one of the benzyl groups since cleavage of a mono benzyl group selectively seemed reasonable, but proved unsuccessful. Secondary amine **97** can then be *N*-alkylated via a facile non-racemizing route using ethyl tosylate and 1,2,2,6,6-pentamethylpiperidine in anhydrous toluene.[86] Unmasking by hydrogenolysis gave *N*-ethyl valine (**98**). A plethora of other *N*-alkyl and *N*-aryl protecting groups are also known, but are not as popular as the *N*-benzyl group.

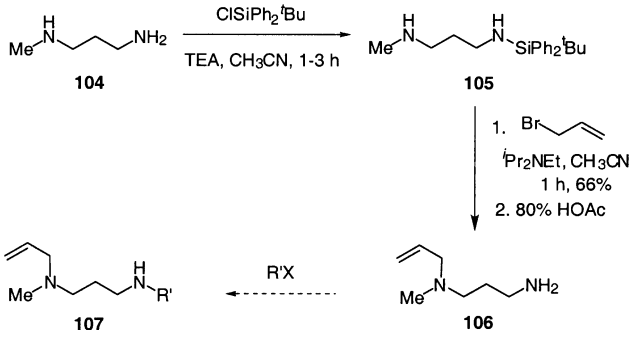
The bulky triphenylmethyl group (trityl or Tr) has been used



Scheme 24.



Scheme 25.



Scheme 26.

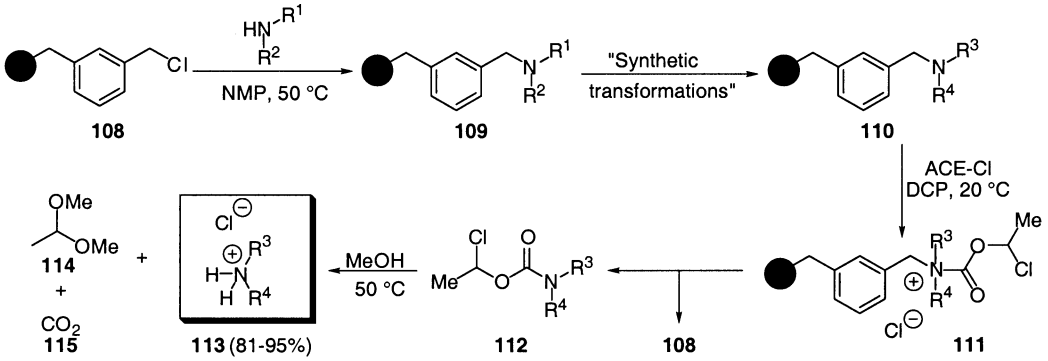
to protect a variety of amino acids, penicillins, and cephalosporins.[87] Protection is usually accomplished using TrCl and Et_3N at 25°C, and detritylation can be performed by action of acidic solution (HCl, acetone), HOBt, or aqueous TFA. Hydrogenolysis (H_2, Pd black, EtOH) has also been a reputable unmasking tool. As demonstrated in Scheme 25, Nakajima reported a synthesis of optically active L-aziridine 2-carboxylic acids using this amino-protecting group.[88] Starting from L-Ser-OBn (**99**), the free amine was tritylated at low temperature to afford protected amino acid **100**. Subsequent tosyl protection, followed by trityl deprotection using TFA, yielded aziridine **102**, which was coupled in high yield with CBz-GlyOH using DCC.

Since silicon is reminiscent of carbon, *N*-silane (N-SiR_3) protecting groups can be considered to be analogs of *N*-alkyl derivatives.[89] Simple examples of common silyl protecting groups are *N*-$SiMe_3$ (*N*-TMS)[90] and *N*-$SiMe_2{}^t$Bu (*N*-TBDMS).[91] A representative preparation includes treating the amine with chlorotrimethylsilane and an organic base such as Et_3N or pyridine. One common drawback of the silyl-protecting group is its highly sensitive nature to hydrolytic cleavage, therefore strictly anhydrous conditions are needed.[92]

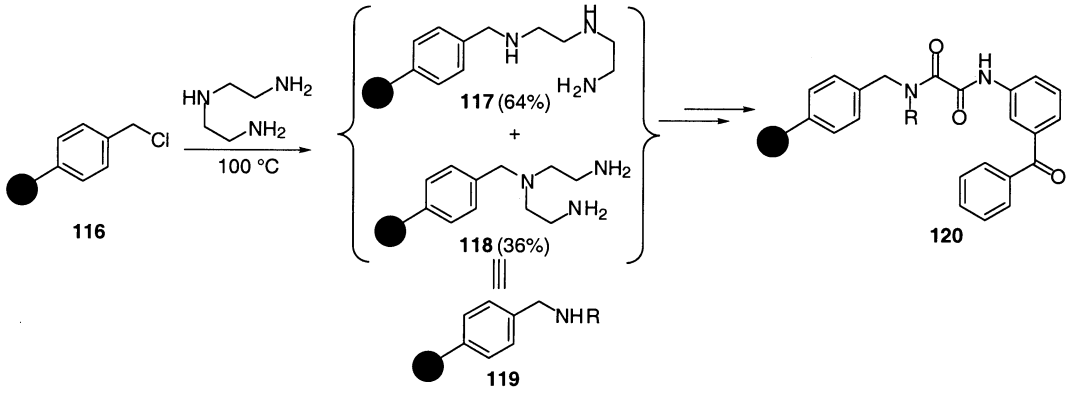
The more sterically demanding silylamines including *N*-$SiPh_2{}^t$Bu (*N*-TBDPS)[93] and *N*-$Si{}^i Pr_3$ (*N*-TIPS) are known to be more stable.[94] *N*-TBDPS groups are stable under hydrolytic and strongly basic conditions, however, the amine nitrogen is often rendered unreactive to additional alkylations due to steric congestion, which can be a pitfall in syntheses of complex nitrogen containing organic compounds. However, on a positive note, a particularly useful feature embedded in utilizing the TBDPS group is selective functionalization of a secondary amine in the presence of a primary amine. As demonstrated by Overman, *N*-methyl-1,3-propanediamine (**104**) was easily silylated at the primary amine, affording the respective secondary silylamine at room temperature to generate intermediate **105**. Silylamine **105** cleanly underwent *N*-allylation using 1 equiv. of allyl bromide with 10 equiv. of diisopropylethylamine in the presence of acetonitrile to afford the corresponding TBDPS secondary amine after 1 h in 66% yield.[93] Deprotection using acetic acid (80% HOAc) can liberate the primary amine **106** in excellent yield, which can be subjected to additional alkylating reagents in order to functionalize the diamine further (Scheme 26).

2.1.4. Solid phase synthesis. As elaborated in the introduction, many drugs contain the secondary amine functionality, which creates the need for their rapid preparation and screening for biological activities. Combinatorial chemistry has demonstrated much potential for preparing targets faster than classical synthetic methods, and in particular, solid-phase organic synthesis of secondary amines is highly suited for such an approach. Although synthesis on solid supports is marked by easy purification procedures, one disadvantage lies in the development of an appropriate linker, which needs to be easily cleaved in a traceless fashion. A widely used attachment of amines to resins is by linkage through a benzyl carbamate since these intermediates are known to be stable under diverse conditions. Another amine linker, reminiscent of trityl, is also commonly used, however, is sensitive to acidic conditions. Recently, it was shown that tertiary amines can be prepared via solid phase synthesis in the absence of a linker to the resin other than the amine itself.[95] Leysen described a similar approach for the synthesis of secondary amines.[96] As delineated in Scheme 27, a generic secondary amine was ligated to the Merrifield resin (**108**) to give tertiary amine **109**, at 50°C for 17 h using NMP as the solvent. Cleavage from the polymer support was accomplished using α-chloroethyl chloroformate (ACE-Cl) providing carbamate product **112**, which upon simple treatment with MeOH at 50°C released the secondary amine as the hydrochloride salt (**113**) in high yields, along with volatile products (**114** and **115**).

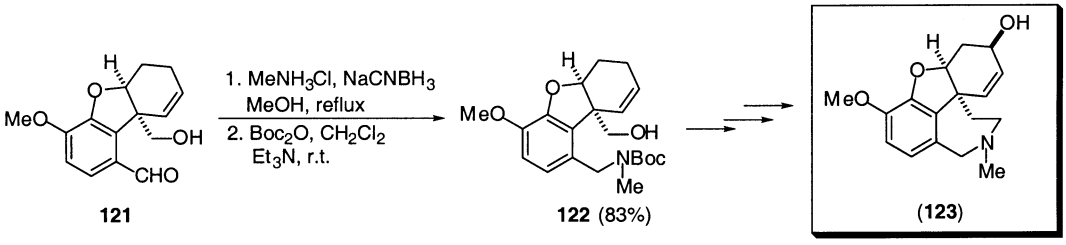
Similarly, this strategy is applicable to polyamines as demonstrated by Parlow.[97] Merrifield resin (**116**) was heated at 100°C with diethylenetriamine for 4 h, followed by gentle rinsing with base, to furnish a mixture of secondary and



Scheme 27.



Scheme 28.



Scheme 29.

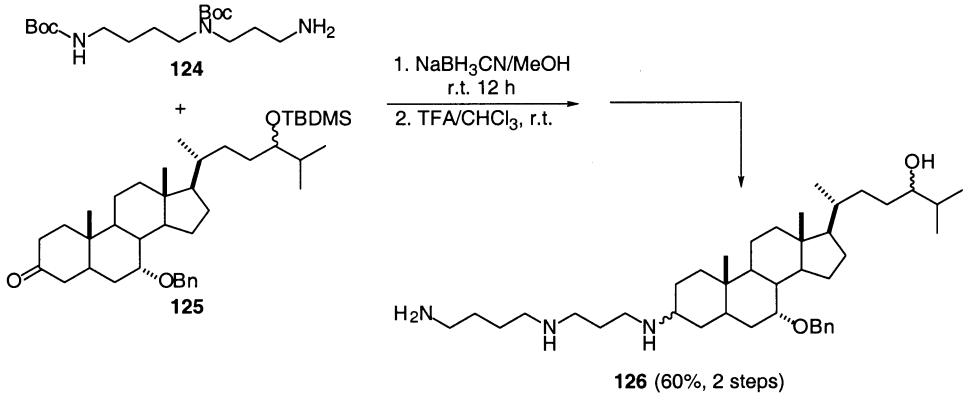
tertiary amines. Combustion analysis of the polymer-bound amine indicated a ratio of 64% monoalkylation product **117** and 36% dialkylation product **118**, respectively. Polymer bound polyamine **117**, which is commercially available, is used in the purification of chemical libraries by complementary molecular reactivity and molecular recognition (CMR/R) strategies. Using the mixture of **117** and **118**, which is represented in generic form **119**, various analogs of heterocyclic carboxamides such as **120** can be accomplished through a simple amide bond formation with the resin bound amine. Upon cleavage from the resin, various compounds showing herbicidal activities can be generated. (Scheme 28).

2.2. Additions to imines, aziridines, and carbonyls

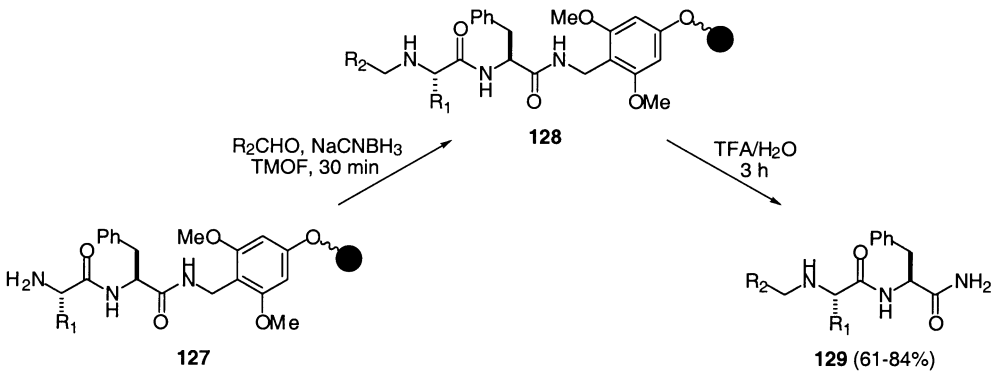
2.2.1. Hydride addition (reduction)

2.2.1.1. Reductive alkylation via imines. One of the most convenient methods for secondary amine formation involves the complete reduction of certain functionalities using a variety of reducing agents. A comprehensive review has been published[98] that covers reductive methods for the production of secondary amines and should be consulted accordingly for further details.

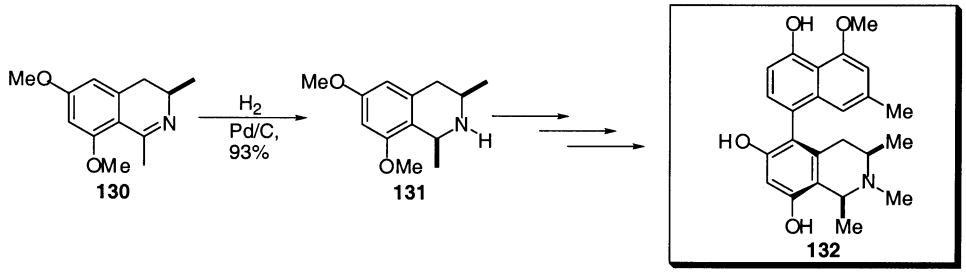
Reductive alkylation in which a primary amine is treated with an aldehyde or a ketone in the presence of a suitable reducing agent (e.g. $NaCNBH_3$) represents one of the most widely utilized methods to prepare secondary amines.[99] Although a rather capricious reaction, can be particularly inefficient since overalkylation readily occurs. Other reducing methods include catalytic hydrogenation,[100] sodium borohydride,[101] iron pentacarbonyl and alcoholic KOH,[102] BH_3-pyridine,[103] and formic acid.[104] Solution phase strategies circumvent overalkylation by using less than 1 equiv. of the carbonyl component relative to the



Scheme 30.



Scheme 31.

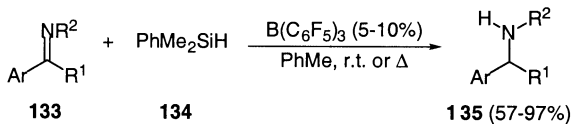


Scheme 32.

amine.[105] For example as depicted in Scheme 29, Trost recently reported a reductive amination of aldehyde **121** by formation of the imine with methylamine followed by reduction with sodium cyanoborohydride in an enantioselective total synthesis of (−)-galanthamine (**123**).[106] The resulting secondary amine was then trapped as the protected *tert*-butyl carbamate **122** in high yield (83%).

Likewise, the polyamino side chain of the antibiotic squalamine (**126**) was easily installed by reductive amination using ketone **125** with Boc protected spermidine (**124**), as represented in Scheme 30.[107] Treatment with TFA affected simultaneous deprotection of the Boc and TBDMS groups to afford a mixture of α- and β-isomers in 60% yield over two steps.

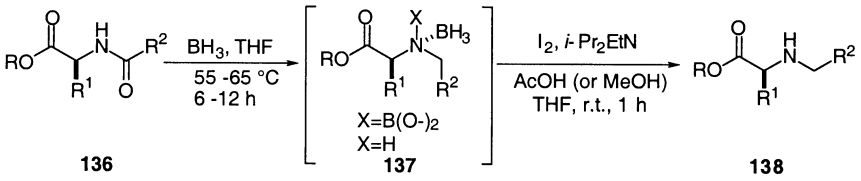
Mono-*N*-alkylation of amino groups by reductive alkylation can also progress smoothly on solid phase, as delineated in Scheme 31. A representative example presented by Campbell uses amino acid dimers containing phenylalanine at the carboxy terminus attached to a solid support.[108] Alkylation of Phe–Phe or Val–Phe dimer on PAL resin **127** treated with numerous aldehydes and $NaCNBH_3$ in neat trimethylorthoformate (TMOF) gave rise to intermediate **128**. Upon cleavage with aqueous TFA and further purification, *N*-alkyl dimers **129** could be obtained in outstanding yields.



Scheme 33.

The reduction of imines (or Schiff bases) is a very convenient and explicit route to the synthesis of substituted amines.[109] However, difficulties may be encountered partly due to imine instability, which makes it cumbersome to easily access the imine in its pure form. As a representative example, in Chen's total synthesis of (*ent*)-korupensamine D (**132**), cyclic imine **130** was reduced using H_2 and 10% Pd/C, which gave rise to *cis*-configured **131** in 93% yield as the only observable diastereomer (Scheme 32).[110] As an alternative approach in another reported synthesis, secondary amine **131** was generated in high diastereoselectivity (ds>95%) using sodium borohydride.[111] Likewise, the reduction of sulfinimines with $LiAlH_4/Me_3Al$[112] and iminophosphoranes using $NaBH_4$[113] can be utilized in much the same manner. This procedure gave rise to the formation of secondary amines in moderate to good yields, and offered alternatives to traditional synthetic procedures.

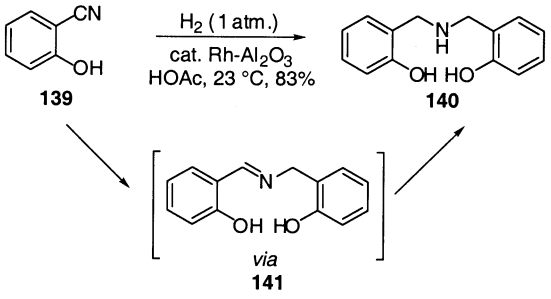
2.2.1.2. R_3SiH addition to imines. Most methods for the reduction imines as mentioned above involve employing borohydride reagents or transition metal hydrogenation catalysts. Although, few general methods using main group Lewis acid catalysts have been reported. An interesting preparation for a diverse range of secondary amines from imines was recently reported by Piers as shown in Scheme 33.[114] In this legend, $B(C_6F_5)_3$ was employed as a catalyst (5–10 mol%) in conjunction with $PhMe_2SiH$ (stoichiometric amount) to hydrosilate a broad range of imines **133** (benzaldimines and ketimines) via a silyliminium intermediate, offering the analogous secondary amines **135** in good to excellent yields upon desilylation. The rates for hydrosilation were reported to be dependent on temperature and the nature of the substituent (R^2) on the imine.



Scheme 34.

2.2.1.3. Hydride addition to carbonyls. The reduction of amides,[115] specifically peptides, and imides[116] is often an alternative approach to reductive alkylation. Reagents typically utilized in these reductions are aluminum hydrides[117] and borohydrides.[118] In the case of borohydrides in the presence of additives such as Lewis or protic acids usually are employed.[119] Although diborane is one of the most common reagents for the synthesis of secondary amines, its traditional work-up procedures are often cumbersome.[120] To affect cleavage of the resulting borane–amine adducts, strongly acidic conditions (refluxing aqueous 1N HCl) are required, which are not compatible with reactions on solid supports.[121] Comparatively, if strongly basic protocols for dissociation of such adducts are carried out, they usually require extended reaction times and high reaction temperatures. Since these harsh conditions can commonly cause epimerization, therefore mild alternatives have been sought.

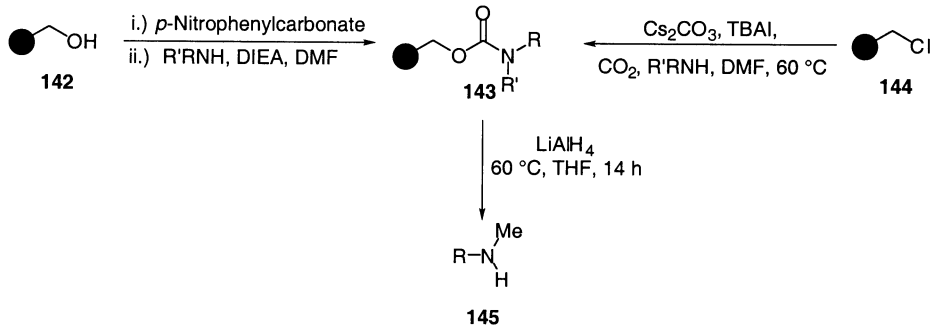
For example, Hall reported a mild and practical oxidative work-up procedure for the synthesis of secondary amines **138** from the corresponding diborane reduction of secondary amides **136** using a basic-iodine solution to promote fast oxidative cleavage of boron-amine intermediate **137** (Scheme 34).[122] This preliminary account discloses both solution and solid phase syntheses of *N*-alkylamino acids and chiral oligoamines derived from peptides.



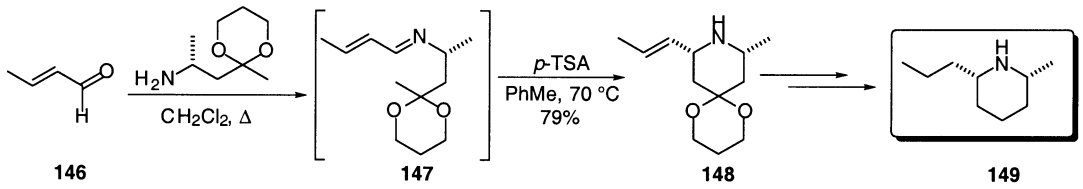
Scheme 35.

Synthesis of secondary amines can also be accomplished efficiently by reduction of nitrile functionality in the presence of a hydride source.[123] $LiAlH_4$,[124] $^{i}Bu_2AlH$,[125] and $NaBH_4$[126] have all served as efficient reductants, although catalytic hydrogenation is the most commonly utilized.[127] However, this protocol does not proceed without its problems, usually resulting in a complex mixture of primary, secondary, and tertiary amines. The composition of the reduction products depends markedly on the nature of the metal catalyst used,[128] reaction temperature,[129] hydrogen pressure,[130] and the structure of the nitrile.[131] Mendoza reported a convenient preparation of secondary amines from nitriles using a rhodium catalyst in the presence of acetic acid at ambient temperature, as delineated in Scheme 35.[132] Reaction conditions appear to be general where aromatic, heteroaromatic, and aliphatic nitriles were hydrogenated to the corresponding secondary amines. Secondary amines such as **140** were generated in good yields (70–95%) by an acetic acid promoted condensation via an isolable intermediate **141**. No tertiary amine formation was detected whatsoever, and further embedded functionality such as ester and hydroxyl moieties were tolerant to these reaction conditions.

N-Methylated amines hold critical importance in amine chemistry.[133] Nevertheless, *N*-methylation of primary amines is quite a difficult task to carry out, and direct *N*-alkylation using methyl iodide or dimethylsulfate fails to provide dialkylamines in good yield.[134] For this reason, reductive methods to date are the most widely utilized.[135] In general, treatment of a primary amine with acetic anhydride and formic acid, followed by borane reduction, affords *N*-methylated amines.[136] Similarly, reduction with $NaBH_4$ after treatment of a primary amine with triethyl orthoformate gives rise to methylated secondary amines accordingly.[137] However, carbamate reduction offers the most expeditious route to form such moieties where LAH traditionally is the reagent of choice.[138] Additional hydride sources have been explored as well.[139] Ho recently exploited LAH reduction of carbamate ligated resin **143** for preparing



Scheme 36.



Scheme 37.

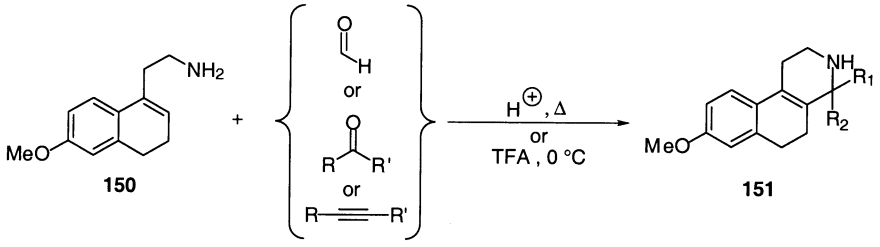
N-methylamines **145** in moderate to good yields, with high purity of products.[140] Carbamate resin **143** is easily prepared from the commercially available Wang resin (**142**) or Merrifield resin (**144**), respectively (Scheme 36).[141,142] Furthermore, as an alternative approach, Ram recently reported a solution phase method for the regio-and chemoselective formation of the C–N bond via carbon dioxide incorporation.[143]

2.2.2. Other nucleophilic addition

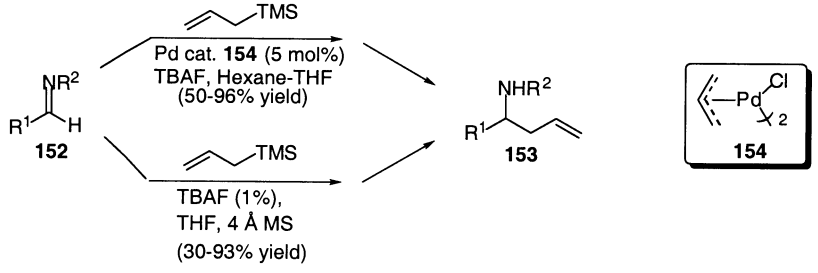
2.2.2.1. With carbon nucleophiles. In addition to reductive alkylation, the addition of resonance stabilized nucleophiles such as enols and enolates to functionalized derivatives such as imines (e.g. *N*-benzylidene) or iminium salts is also a popular route towards secondary amine synthesis.[144] One such example is a Mannich-type reaction.[145] An interesting report was recently descrbed by Troin in the synthesis of dihydropinidine (**149**), which is an important alkaloid of the Mexican bean beetle *Epilachna varivestis* (Coccinellidae).[146] Given their approach, crotonaldehyde (**146**) underwent a Mannich-type reaction with an amino ketal, furnishing secondary amine **148** (79%; de>95%) after gentle treatment of the intermediate imine **147** with *para*-toluenesulfonic acid at 70°C in toluene for 12 h. Further modification, deprotection, and isolation as the hydrochloride salt, offered (+)-dihydropinidine (**147**) as depicted in Scheme 37.

Another example includes the preparation of cyclic secondary amines through a Pictet–Spengler cyclization.[147] As seen in this account, imines are utilized as key intermediates in secondary amine synthesis. This acid-catalyzed intramolecular cyclization of intermediate imines gives rise to 1,2,3,4-tetrahydroisoquinoline derivatives. This common name reaction has been extensively studied, and its scope has been applied in the context of several heterocyclic syntheses. Recently, Katzenellenbogen reported a two-step vinylogous Pictet–Spengler cyclization using a variety of activated aldehydes, ketones, and alkynes in order to prepare numerous substituted hexahydrobenzo[*f*]isoquinolines in high yields.[148] A unique set of reaction conditions was investigated to achieve efficient cyclization with acid-sensitive electrophiles, which is an added benefit of this procedure. As portrayed in Scheme 38, dihydronaphthylamine (**150**) reacted with various classes of functionality including aldehydes, ketones, and alkynes. After 24 h, the corresponding hexahydrobenzo[*f*]isoquinoline **151** could be isolated accordingly. In a similar account, Ohwada recently developed a prototype Pictet–Spengler reaction of imines of 2-phenethylamine catalyzed in superacid media (TFSA) to give parent and 1-substituted 1,2,3,4-tetrahydroisoquinolines in moderate to high yields.[149]

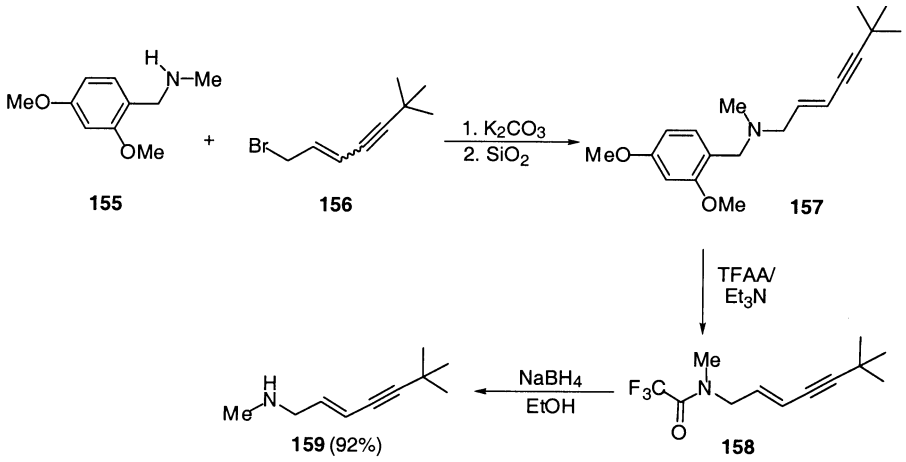
Secondary allylamines are widely used as key intermediates due to their critical importance in the area of organometallic reactions, specifically in the area of asymmetric synthesis. They are generally prepared by addition of allyl organometallic reagents (e.g. allylstannanes) to imines in the presence of a catalyst, typically a Lewis acid.[150] Various reviews on the use of a wide array of catalysts and conditions have appeared.[151] As such, only a brief discussion on this subject will be made herein. As depicted in Scheme



Scheme 38.



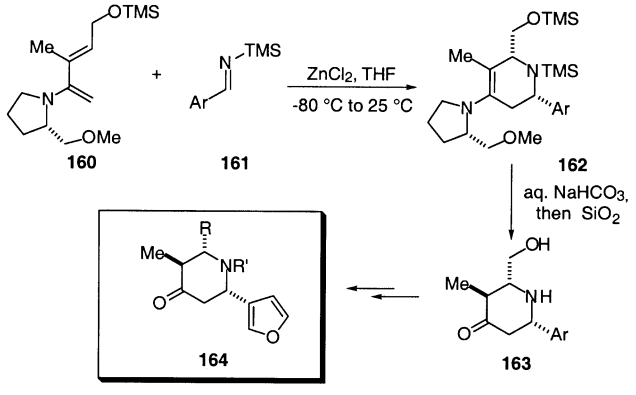
Scheme 39.



Scheme 40.

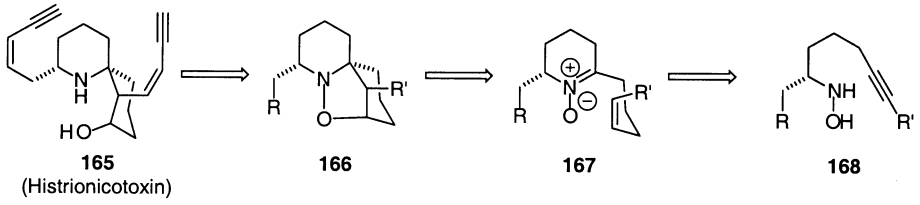
39, Yamamoto recently reported a novel allylation of imines **152** using allyltrimethylsilane as a replacement for the more toxic stannyl counterpart, in the presence of a palladium-TBAF cocatalyst system.[152] This system was considerably more beneficial from the point of 'green chemistry', and the yields of allylamines **153** were typically good. However, these reactions were noted to be quite sluggish when devoid of the palladium catalyst. In another account, Hou reported a similar transformation wherein treating imine **152** with allytrimethylsilane in the presence of tetrabutylammonium fluoride gave the corresponding homoallylamines **153** in 30–93% yields.[153] Notably, instead of heavy metal catalysts or strong Lewis acids, the catalytic role of the fluoride ion was recognized from their mechanistic studies, to effectively trigger the allylation.

Substituted allylamines as mentioned are commonly formed via metal catalyzed reactions. However, as an alternative approach, Nussbaumer recently reported a highly attractive and selective TFAA-cleavage reaction of 2,4-dimethoxybenzylamines and its use in the application for the efficient synthesis of secondary amines.[154] TFAA-treatment of various allylic, propargylic, homopropargylic, and *tert*-2,4-dimethoxybenzylic amines leads to a highly selective cleavage of their dimethoxybenzylic C–N bonds. The resultant trifluroacetamides can then be readily converted to the corresponding secondary amines. As shown in Scheme 40, conversion of *N*-methyl-2,4-dimethoxybenzylamine (**155**) with 1-bromo-6,6-dimethyl-2-heptene-4-yne (**156**, *E*/*Z*≈3/1) leads to a mixture of *N*-(2,4-dimethoxybenzyl)-6,6-trimethyl-2-hepten-4-ynamines (157, *E*/*Z*≈3/1), which was readily separable by chromatography. Treatment of **157** with TFAA/Et_3N produced trifluoroactamide **158** in nearly quantitative yield. Further deprotection was accomplished using sodium borohydride in ethanol to give the corresponding secondary amine **159** in high yield.

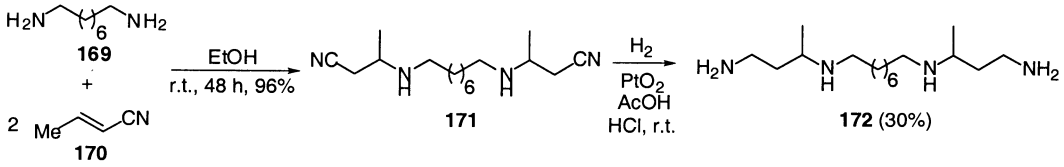


Scheme 41.

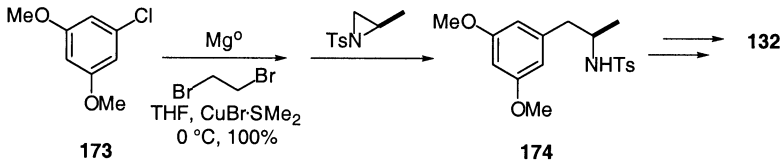
Besides the isoquinoline moiety (Scheme 38), piperidine-bearing alkaloids display a wide range of biological activities and in many cases they are scarcely available from natural sources. The structural motif common to nuphar alkaloids **164** is the presence of a trisubstituted piperidine ring moiety. As demonstrated in Scheme 41, Barluenga recently explored a powerful approach to this cyclic secondary amine via an asymmetric Diels–Alder cycloaddition, which is another useful method towards the synthesis of secondary amines.[155] Chiral 2-aminodiene **160** reacts with aromatic *N*-trimethylsilylaldimines **161** in the presence of a mild Lewis acid ($ZnCl_2$), to afford, after mild hydrolysis of the [4+2] cycloadduct **162**, 4-piperidones **163** in high enantiomeric excesses. This piperidone substrate is a



Scheme 42.



Scheme 43.



Scheme 44.

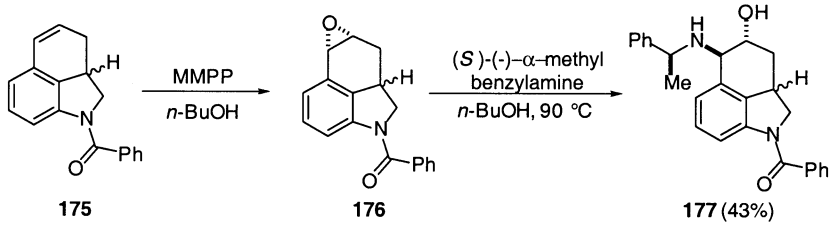
suitable intermediate towards the total synthesis of nuphar alkaloids (**164**).

The secondary amino group on the piperidine skeleton can also be fashioned as nitrones, which are synthetically useful intermediates. For example, Holmes reported a synthesis of (−)-histrionicotoxin (**165**) using a series of intramolecular processes.[156] As demonstrated retrosynthetically in Scheme 42, hydroxyl amine–alkyne cyclization of **168** is used to prepare the parent nitrone **167**, which is intercepted by a [3+2] cycloaddition to afford **166**. Reduction of the strained N–O bond by treatment of **166** with activated Zn dust in glacial acetic acid for 30 min efficiently affords the spirocyclic structure of natural product **165** in 98% yield.

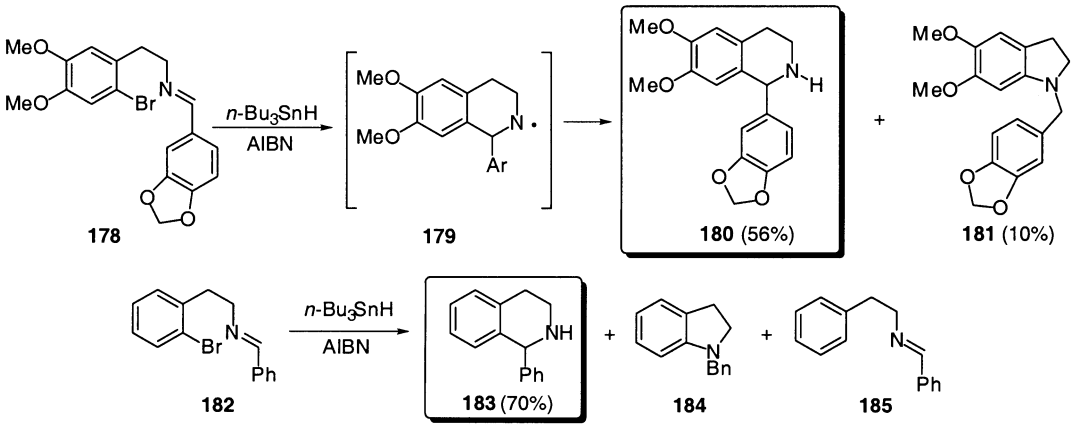
The addition of amines to unsaturated functionality is also a powerful method toward the synthesis of secondary amines, which is commonly known as a Michael Addition.[157] As illlustrated in Scheme 43, Edwards demonstrated that 1,8-diaminooctane (**169**) reacted with 2 equiv. of acrylonitrile (**170**) at room temperature to afford diamine **171** in high yield using ethanol as the solvent.[158] Reduction of both cyano moieties via hydrogenation yielded the corresponding tetramine **172**. Although efficient, Michael additions are not free from practical problems, where overalkylation still proves bothersome resulting in a mixture of mono- and dialkylated products.

The reaction of aziridines and aziridinium ions with nucleophiles is another important transformation for the preparation of derivatized secondary amines, yet it is underutilized in organic synthesis. A short review article has been published regarding this subject.[159] As shown in Scheme 44, ring opening of (*R*)-*N*-tosylaziridine with the Grignard reagent derived from **173** in the presence of $CuBr{\cdot}SMe_2$ resulted in the formation of secondary amine **174** in quantitative yield. This novel approach towards the efficient preparation of enantiomerically pure amines was well utilized as the key step in the first total synthesis of the natural product korupensamine D (**132**).[160]

2.2.2.2. With nitrogen nucleophiles. β-Amino alcohols are a novel class of organic compounds that of considerable interest in medicinal chemistry, and comprehensive review articles have been published focusing on their preparation.[161] In conjuction with the development of diastereoselective and enantioselective synthesis of these compounds, oxirane ring opening reactions by nitrogen nucleophiles have become a versatile route to various secondary amino alcohols. The most practical and widely used method for the synthesis of these compounds is the direct aminolysis of 1,2-epoxides.[162] However, this synthetic transformation is usually carried out with a large excess of ammonia or amine at elevated temperatures, and a drawback is that the reaction usually fails when poorly nucleophilic amines are used. Several modifications of this classical procedure have been reported, but the most common involves the use of a variety of activators such as Lewis acids or metal salts to effect the ring opening at room temperature.[163] Under neutral or basic conditions, amine nucleophiles generally attack the sterically less hindered carbon atom of the epoxide. In order to facilitate the regioselectivity of the epoxide ring opening, variations in procedure have been devised. As an example, Kress, Martinelli, and Varie published their synthetic efforts toward Ergot alkaloid LY228729.[164] Epoxide **176**, which was generated from the corresponding olefin **175** using MMPP, was dissolved in *n*-butanol, and (*S*)-α-methylbenzylamine was added to the solution and heated overnight at 90°C. After 24 h, the reaction mixture was



Scheme 45.



Scheme 46.

allowed to cool whereupon amino alcohol **177** selectively crystallized from the reaction mixture as a single isomer (Scheme 45). Regioselective opening of the corresponding epoxide ring occurred by attack of the primary amine at the less hindered carbon of the oxirane.

2.2.2.3. With carbon radicals. The chemistry of nitrogen centered radicals has received considerably less attention than the carbon centered species, but their generation and reactions have been well studied.[165] Nitrogen systems have attracted much attention due to their capacity of incorporating a heteroatom in the cyclization step, thus exerting considerable promise in the synthesis of various heterocycles and amines having medicinal applications. Aminyl radicals are marked as being nucleophilic species. Takano and coworkers reported an intramolecular addition of the nucleophilic nitrogen centered radical onto an imine double bond as a key step in their synthesis of cryptostyline alkaloids (Scheme 46).[166] Cyclization of aryl bromide **178** gave the isoquinoline skeleton **180** in 56% yield via aminyl radical intermediate **179**, which was generated through a 6-*endo* addition to an imine carbon center. Competitive 5-*exo* cyclization was a minor side reaction and afforded the dihydroindole **181** in low yield. Likewise, this pattern of reactivity has been noted by Warkentin, who reported a large 6-*endo* preference for the cyclization of an aryl radical onto an aldimine.[167] Cyclization of the radical derived from bromide **182** afforded a 70% yield of secondary amine **183**, while minor amounts of 5-*exo* cyclization product **184** and simple reduction product **185** were also obtained.

3. Preparation of secondary aromatic amines

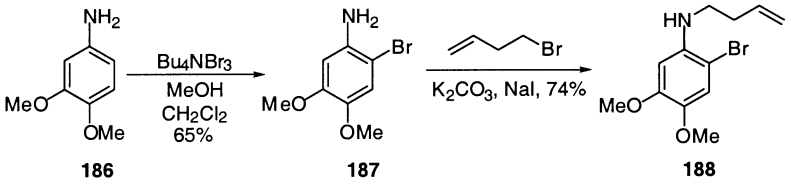
3.1. Introduction

Aromatic secondary amines play a key role in a number of fields.[168] These include industrial, pharmaceutical, and agrochemical applications. On an industrial level, these compounds have served as antioxidants in petrochemicals for polymer and rubber manufacturing processes.[169] Also, they have served well in applications such as photography, xeroxography, pigments, dyes, and electronic materials.[170] Additionally, aryl amines can be useful in small quantities as additives to gasoline in that they substantially improve the octane rating.[171] More importantly, *N*-alkylated aromatic amines are also well utilized in the synthesis of numerous pharmaceutical compounds. One of the most revealing facts are that a significant number of the twenty top-selling pharmaceuticals in 1994 contained aromatic carbon–nitrogen bonds.[172]

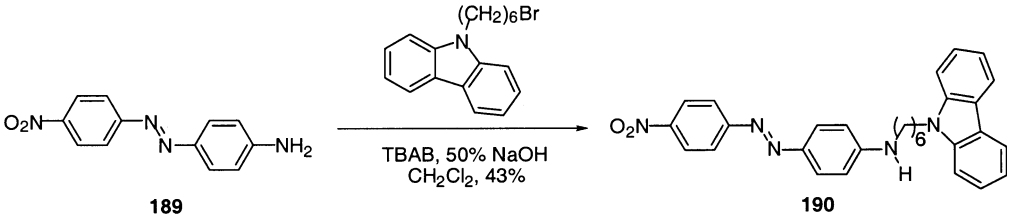
3.2. *N*-Alkylation of primary aryl amines

3.2.1. Unactivated aryl amines

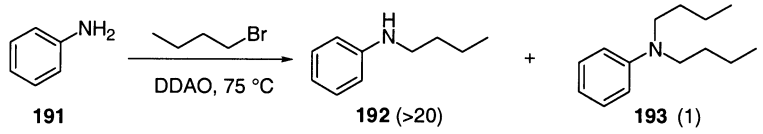
3.2.1.1. With alkyl halides. The *N*-alkylation of aromatic amines is usually carried out by the treatment of an amine with an alkyl halide in the presence of a base (usually potassium carbonate), and in some cases with the addition of potassium iodide to promote the reaction.[173] However, selective synthesis of *N*-alkylanilines is often intricate due to the difficulty in preventing the formation of the corresponding *N*,*N*-dialkylaniline. Direct alkylation with excess aniline in the presence of an alkyl halide is not feasible in order to prepare secondary amines in good yields simply because the formation of tertiary amines and quartenary ammonium salts is usually the dominant reaction process. Therefore, this procedure lacks in fanfare and remains far from general use. Physical organic concepts in the light of basicity, nucleophilicity, electronic and steric effects have all been well examined in order to help explain the course of alkylations of aromatic amines. Buchwald demonstrated this useful synthetic transformation in his novel syntheses



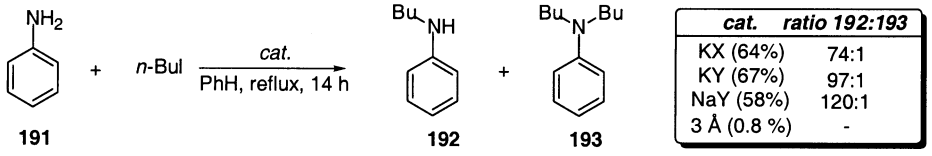
Scheme 47.



Scheme 48.



Scheme 49.

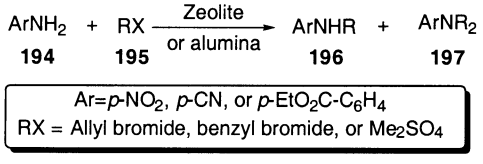


Scheme 50.

of tetrahydropyrroloquinolines. Bromination of 4-aminoveratrole (**186**) with Bu_4NBr_3, followed by mono-*N*-alkylation using 4-bromo-1-butene with K_2CO_3 and NaI as a promoter, afforded the dialkylamine **188** in high yield (Scheme 47).[174]

Enomoto reported an *N*-alkylation procedure catalyzed by additives such as ammonium halides.[175] In a similar manner, Dehmlow found that the alkylation of aromatic amines in the presence of inorganic bases (e.g. crushed NaOH) is accelerated by a phase transfer catalyst (Bu_4NHSO_4, *n*-Bu_4NBr, or *n*-hex_4NBr).[176] It was apparent that the phase transfer catalyst accelerated the reaction rate by three to four-fold for aromatic amine alkylation. However, under these conditions aliphatic amines did not undergo the same transformation. In a similar fashion, a highly selective and direct mono-*N*-alkylation of Disperse Orange (**189**) with a carbazole alkyl bromide utilizing aqueous sodium hydroxide and tetrabutylammonium bromide (TBAB) as a phase transfer catalyst was published.[177] The target molecule **190** was prepared in 43% overall yield with only trace amount of the overalkylated product (Scheme 48).

Likewise, Rathman utilized an aqueous micellar surfactant as a catalyst in the selective *N*-alkylation of aniline, which was found to be highly chemoselective for monoalkylation as shown in Scheme 49.[178] The observed increase in reaction rate results from increased reactant solubilization as well as a conducive micellar environment. The reaction of aniline

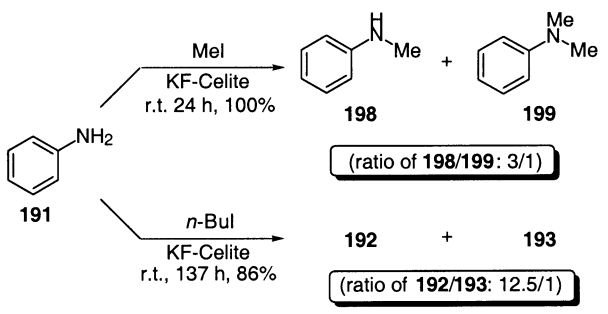


Scheme 51.

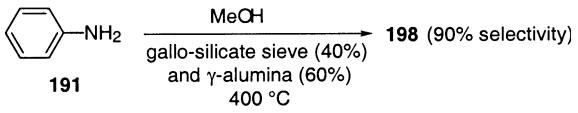
(**191**) with 1-bromobutane using a single phase nonionic aqueous dimethyldodecylamine oxide (DDAO) surfactant at 75°C resulted in high selectivity (>20:1) in favor of the *N*-alkyl product **192**, with accompaniment of relatively small amounts of *N*,*N*-dibutylaniline (**193**).

Alternatively, Onaka and coworkers have reported a highly selective mono-*N*-alkylation of aniline and its derivatives over alkali cation exchanges X- and Y-type zeolites (Scheme 50).[179] The intrinsic pore structures of X- and Y-zeolites are assumed to be responsible for the high selectivity of this reaction. NaY-type zeolites offered the best results where the selectivity was 120:1 in favor of the *N*-butylaniline (**192**). Linde 3 Å zeolites were noted to fail in promoting similar alkylation reactions due to the inherent smaller pore structure. Within these well-defined crystalline aluminosilicate zeolite homogeneous cavities, the crystalline structure can differentiate the molecular shapes of organic reactants and products, thus resulting in high chemoselectivities.

As representatively illustrated in Scheme 51, anilines possessing strongly electron withdrawing groups (e.g. *p*-NO_2), which are often resistant to undergo alkylation



Scheme 52.



Scheme 53.

reactions even with the addition of strong base (KOH), can be successfully *N*-alkylated using this methodology.[180] *N*-allylation, *N*-benzylation, and *N*-methylation of aniline derivatives containing electron-withdrawing functionality all progressed with high selectivity in favor of mono-*N*-alkylated product **196**. High selectivities are inferred to be the result of the *N*-alkylation reaction proceeding within the intercrystalline pores.

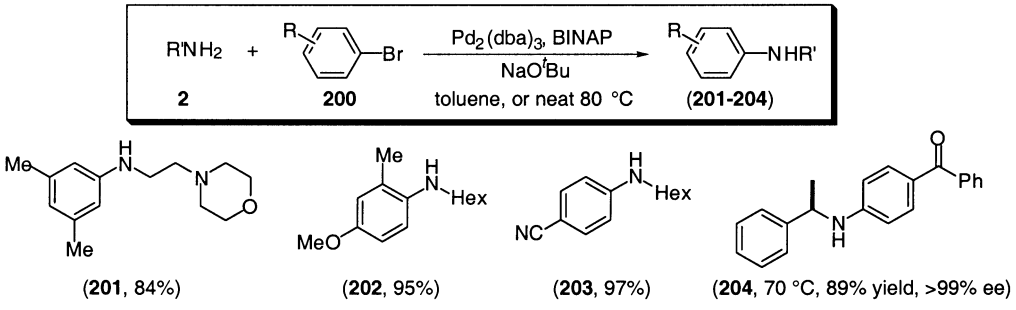
In a similar fashion, Yamawaki reported an effective and mild *N*-alkylation protocol using Celite® coated with potassium fluoride as an effective and economical reagent for the aforementioned transformation.[181] Four moles of aniline (**191**) were treated with a variety of halides (1 mol) including MeI, or *n*-BuI, with 5 mol of KF-Celite® at ambient temperatures to furnish good to high yields of *N*-alkylated products (Scheme 52). Selectivities using both halides were generally high and in favor of the corresponding secondary aromatic amines **198** and **192**, respectively. Furthermore, reaction conditions were mild, and work-up procedures were quite simplistic. This KF-Celite® doped system is considered to be an attractive example of an inorganic solid-supported reagent which catalyzes an organic transformation.

3.2.1.2. With alcohols. Alcohol condensation with aromatic amines in the vapor phase using various catalysts has enjoyed great synthetic utility in the introduction of alkyl functionality on nitrogen. Generally, numerous catalysts have been explored in the reaction of an aromatic primary amine with an alcohol to form a product containing substantially an *N*-alkyl monosubstituted aromatic amine. For example, a wide variety of environmentally safe heterogeneous catalysts have been developed. To list a few, molecular sieves, amorphous silica–alumina, gallosilicates, boron–aluminum, iron phosphate, and aluminum phosphate–alumina catalysts all have enjoyed much success.[182] In addition, metal oxides (e.g. Cu/Zn oxide) catalyze the alkylation of aniline to give *N*-methyl aniline in the presence of hydrogen gas.[182] As an example, 1 mol of aniline (**191**) was *N*-alkylated using 0.75 mol of methanol to produce *N*-methylaniline (90% selectivity; 56% conversion) in the presence of a water-insoluble gallo-silica–alumina catalyst at high temperature. Selectivity in favor of the *N*-alkylamine **198** was excellent, and conversion yields were generally good (Scheme 53).

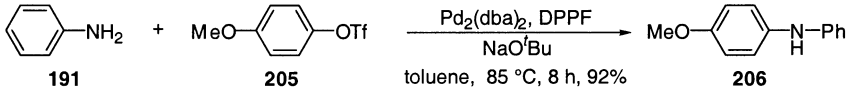
3.2.2. Metal-catalyzed reactions. The palladium-catalyzed arylation of amines have been under the focus of intensive research in recent years.[183] Buchwald and co-workers have made considerable contributions towards the development of general, reliable, and practical catalysts for the formation of aromatic carbon–nitrogen bonds by the cross-coupling of amines and aryl (and heteroaryl) bromides, chlorides or triflates. A recent review details the reaction from both a synthetic utility and mechanistic viewpoint.[184]

The cross coupling of aryl halides **200** with primary amines **2** using a combination of $Pd(OAc)_2$ or $Pd_2(dba)_3$ with BINAP or $Pd_2(dba)_3$ with P(*o*-tolyl)$_3$ in the presence of sodium *tert*-butoxide serves as an excellent catalyst system for the generation of aromatic secondary amines in formidable yields.[184] A typical reaction sequence is depicted in Scheme 54 along with typical secondary aromatic amines (**201**–**204**) formed using the arylation conditions listed starting from the analogous primary amines. Typical solvents used were toluene and THF, but neat reactions have proved successful as well. As a logical extension of this procedure, it should be noted that enantiomerically pure *N*-arylamines such as **204** can also be prepared by a similar intermolecular coupling approach, which was also high yielding and completely stereospecific. Construction of polyanilines holding great promise as electrically conductive polymers has also been quite prosperous by this Pd-catalyzed amination reaction.

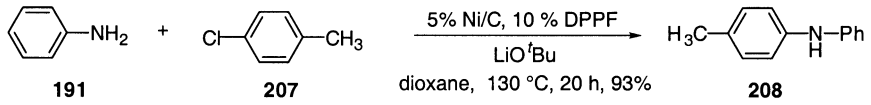
In contrast, Hartwig investigated the addition of anilines to pseudo halides (aryl triflates) catalyzed by a combination of



Scheme 54.



Scheme 55.



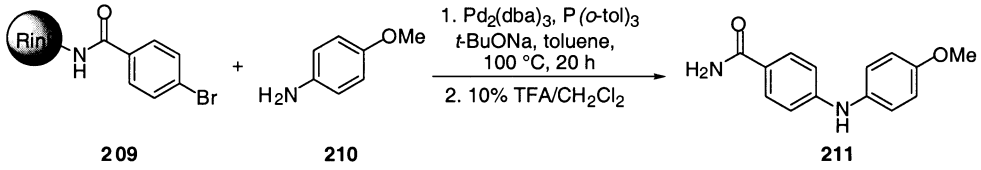
Scheme 56.

$Pd(dba)_2$ and DPPF as the choice of ligand (Scheme 55).[185] As a representative example, reaction of electron rich triflate **205** with aniline (**191**) in the presence of sodium *tert*-butoxide with $Pd(dba)_2$-DPPF in toluene gave high yield (92%) of the mixed diaryl secondary amine **206** after 8 h.

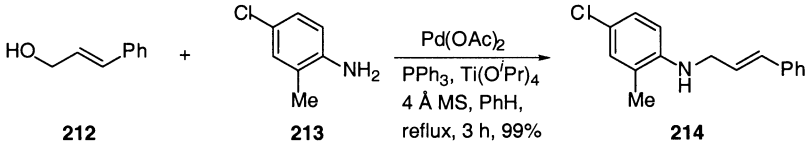
As a complement to the above mentioned protocols, Lipshutz developed a novel heterogeneous aromatic amination protocol, which utilizes inexpensive aryl chlorides using nickel-on-charcoal (Ni/C) rather than palladium as the catalyst (Scheme 56).[186] With LiO^{t}Bu (1.2 equiv.) and aniline (**191**) (2 equiv.) in the presence of Ni/C, *p*-chlorotoluene (**207**) was smoothly converted to the aniline derivative 208 using DPPF. This methodology offers an economically appealing alternative to current palladium protocols.

Solid phase synthesis of aryl amines via a palladium-catalyzed amination of a resin-bound aromatic bromide is an excellent extension of the above cited work. Ward in a recent communication disclosed a method for the generation of aryl secondary amines from aryl bromides using *ortho*- or *para*-anisidines under the palladium(0) catalysis conditions on solid support.[187] As exhibited in Scheme 57, coupling of a bromide linked to a Rink resin (**209**) with *para*-anisidine (**210**) occurred uniformly in the presence of the P(*o*-tol)/Pd system with the addition of sodium *tert*-butoxide. Conversions were complete, and coupled product **211** was cleanly generated within 20 h upon cleavage from the resin using 10% TFA. Nevertheless, much to a surprise, the addition of BINAP in association with P(*o*-tol)$_3$/Pd catalyst resulted in unsuccessful couplings, in which unreacted bromide was recovered intact.

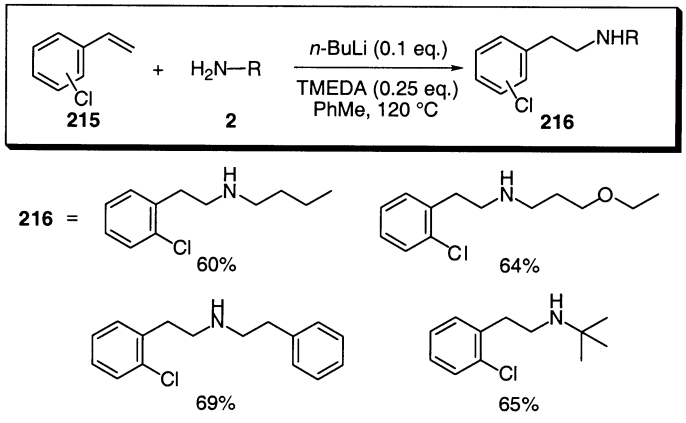
Replacement of aryl bromides with an allylic alcohol in palladium-catalyzed amination reactions involving anilines offers an exceptional method for the formation of *N*-allylanilines.[188] Yang recently investigated a palladium-catalyzed allylation of anilines by the direct use of allylic alcohols in the presence of $Ti(O^iPr)_4$.[189] As presented in Scheme 58, allylic alcohol **212** underwent amination using 4-chloro-2-methylaniline (**213**) resulting in nearly quantitative yield (99%) of the corresponding *N*-allylaniline **214**. Mechanistic details are also presented in this account, in



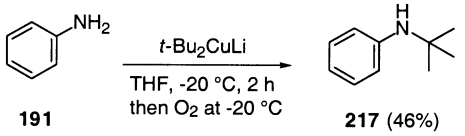
Scheme 57.



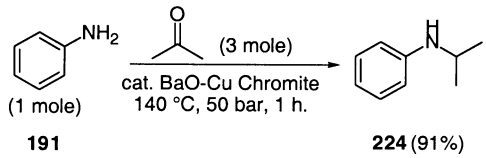
Scheme 58.



Scheme 59.



Scheme 60.



Scheme 63.

which the reaction is postulated to proceed via π-allyl-palladium intermediates.

Recently, Beller and co-workers synthesized various pharamaceutically interesting β-arylethylamines **216** from chlorostyrenes **215** using various primary aliphatic amines via hydroamination in substantial yields in the presence of catalytic amounts of *n*-butyllithium (0.1 equiv.) and 0.25 equiv. of tetramethylethylenediamine (TMEDA) (Scheme 59).[190]

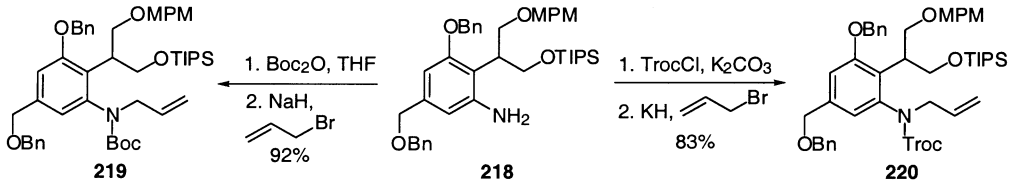
Another mild and efficient novel *N*-alkylation method of amines applies the use of organocopper reagents as illustrated in Scheme 60. Yamamoto desribed an oxidative coupling of lithium alkylcopper amide, which was derived from lithium dialkylcuprates and primary and secondary amines.[191] Despite the fact that alkyl amines can be used under the cited conditions, one of the highest reported yields in this communication for secondary amine formation takes advantage of aniline as the starting amine. Thus, treatment of aniline (**191**) with *tert*-butyl copper reagent formed by reaction of *tert*-butyl lithium and cuprous iodide in THF for 2 h followed by quenching with molecular oxygen gave *tert*-butyl aniline (**217**) in 46% isolated yield.

3.2.3. Protected aromatic amines. Following similar suite, aniline derivatives can be protected and subsequent alkylation can occur in much the same fashion as aliphatic amines. Protection and unmasking methodology follows similarly and will not be reiterated upon again. As prime examples, Martin and coworkers employed two common protecting groups elaborated upon in this review, to protect aromatic amine functionality in their formal total synthesis of (+)-FR900482.[192] As illustrated in Scheme 61, aniline **218** was converted to its *tert*-butyl carbamate derivative using Boc_2O in refluxing THF to afford the secondary amine. *N*-Allylation of the derived anion with allyl bromide provided the *N*-Boc, *N*-allyl protected product **219** in high yield (92%) using sodium hydride as the base of choice. Similarly, utilizing the same substrate **218**, the trichloroethoxycarbonyl group could be introduced accordingly onto the aromatic amine using straightforward techniques. Allylation using potassium hydride gave rise to Troc-protected derivative **220** in 83% yield. Subsequent exposure of carbamate 220 to Zn/HOAc induced removal of the Troc group to afford the free amine. Compound **219** can be unmasked using traditional protocols.

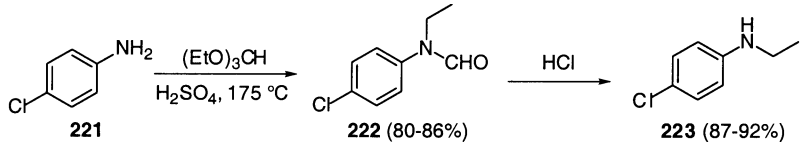
An older but still quite suitable method to effect the mono-*N*-alkylation of primary aromatic amines involves the use of alkyl orthoformates (Scheme 62). Trimethyl or triethyl orthoformate is among the most commonly used, but others can be readily substituted. For instance, heating *p*-chloroaniline (**221**) with commercially available triethyl orthoformate and concentrated sulfuric acid at bath temperature of 175°C for approximately 2 h results in the formation of *N*-ethyl-*p*-chloroformanilide (**222**) (80–86% yield).[193] Further exposure of the formanilide **222** to aqueous hydrochloric acid results in the formation of *N*-ethyl-*p*-chloroaniline (**223**) (87–92%) after neutralization with potassium hydroxide and purification by distillation.

3.3. Additions to imines (reductive alkylation)

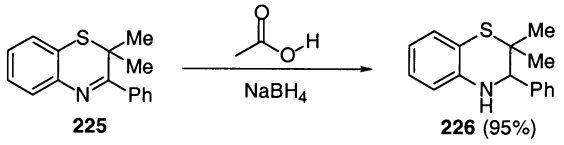
Reductive alkylation has proved to be one of the most straightforward routes to generate secondary amines efficiently in organic synthesis. Various *N*-alkylated anilines can be prepared by reductive alkylation of a primary aromatic amine with different carbonyl compounds using numerous metal catalysts such as platinum, palladium, and rhodium sulfates.[194] Studies on selectivity and reactivity using a copper chromite catalyst in aromatic secondary amine synthesis by a reductive alkylation procedure using primary amines and carbonyl compounds has also been well examined.[195] Pillai reported the reaction of acetone with aniline, and several carbonyl compounds, encompassing



Scheme 61.



Scheme 62.



Scheme 64.

methyl ethyl ketone, methyl isobutyl ketone, benzaldehyde, acetophenone, and benzophenone.[196] The authors stated the reactions proceeded smoothly, and the respective *N*-alkylanilines were obtained in good yields with excellent selectivity. For example, as shown in Scheme 63, the reductive alkylation of aniline (**191**) with acetone (1:3 mol ratio) at 140°C under 50 bar hydrogen pressure for 1 h using freshly pre-reduced copper chromite catalyst gave rise to 91% of *N*-isopropylaniline (**224**) with nearly 100% selectivity. The yields of the secondary amines were correlated with the structure of carbonyl compounds and proved that the reactivity decreased with increased steric hindrance at the carbonyl moiety.

Another interesting method concerning the alkylation of aromatic amines reported by Gribble uses liquid carboxylic acids and sodium tetrahydroborate.[197] Liberatore extended the scope of this method further to the *N*-alkylation of amines with solid carboxylic acids.[198] In the course of this investigation, it was determined that treatment of 1,4-benzothiazines **225** with $NaBH_4$ in neat acetic acid as the solvent, gave rise to the corresponding dihydro-1,4-benzothiazines **226** in high yields (Scheme 64).

4. Conclusion

This review has given a comprehensive survey regarding the synthesis of alkyl and aromatic secondary amines as well as some their synthetic uses. Secondary amines have clearly demonstrated to be extremely useful synthons towards numerous natural products as well as bioactive molecules exhibiting unique properties. The common solution phase synthetic methods towards secondary amine formation have been discussed herein. Recently, the solid phase synthesis of this functionality has gained popularity and possesses great potential leading to compound diversity such as the generation of combinatorial libraries and drug discovery.

Outstanding regioselectivity and chemoselectivity have been noted in numerous examples, and such aspects as differentiation in multifunctional groups is presumed to be a salient feature. Due to these versatilities, secondary amines have been frequently employed as excellent intermediates in further syntheses, and hold a plethora of industrial applications. This important functional group class, although quite popular, still holds great potential such that new synthetic methods are constantly emerging. Therefore, amine chemistry undoubtedly will be charted for further exploration in the future.

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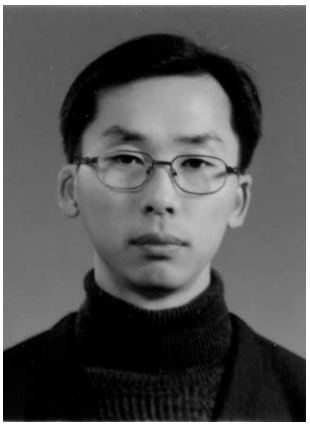

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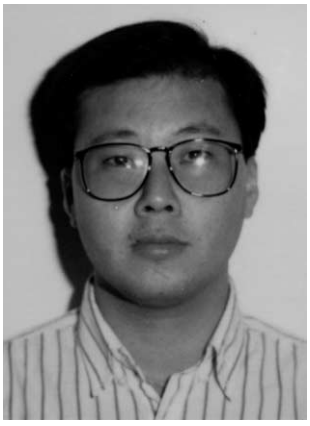

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